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Methylprednisolone combined with low-dose indomethacin treating acute fibrinous and organizing pneumonia after a surgical resection of rectal adenocarcinoma: a case report and literature review

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Abstract. – OBJECTIVE: Acute Fibrinous and Organizing Pneumonia (AFOP) is a new pathologic pattern of acute lung injury characterized by the presence of intra-alveolar fibrin in the form of fibrin "balls" in a patchy distribution.

CASE REPORT: A 65-years-old female after a surgical resection of rectal adenocarcinoma presented with typical manifestations of hospital-acquired pneumonia, but she didn't respond to the anti infective therapy. After an explicit diagnosis of AFOP via percutaneous needle lung biopsy, she got an impressive improvement with a long-term therapy of methylprednisolone and low-dose indomethacin. To date, a total of non-overlapped 45 individual AFOP cases and 4 single-center studies involving AFOP have been reported. The most common coexisting diseases are infections, connective tissue diseases and hematological diseases. Corticosteroids and immunosuppressants are the most common agents prescribed in AFOP. The prognosis of AFOP is unfavorable, associated with the pathologic characteristics and the clinical parameters.

CONCLUSIONS: The immune system activated by infection may play an important role in the pathogenesis of AFOP. Low-dose indomethacin combined with methylprednisolone may be a new choice for AFOP treatment.

Key Words
Acute fibrinous and organizing pneumonia, Acute lung injury, Corticosteroid, Indomethacin.

Acute Fibrinous and Organizing Pneumonia (AFOP) was initially reported in 2002 as a novel pathologic pattern that didn't meet the criteria for classical patterns of acute lung injury, namely, diffuse alveolar damage (DAD), organizing pneumonia (OP), or eosinophilic pneumonia (EP)[1]. The dominant finding was the presence of intra-alveolar fibrin in the form of fibrin ''balls'' in a patchy distribution with an average of 50% airspace involvement. Loose connective tissue consisting of fibroblastic plugs was observed within the alveolar ducts and bronchioles. To date, the pathogenesis of AFOP remains unclear, and there is no consensus on the standard treatment.

Herein we present a female with a recent surgical resection of rectal adenocarcinoma, whose symptoms and radiological features mimicked typical hospital acquired pneumonia (HAP), but not responding to the anti infective therapy. A percutaneous needle lung biopsy (PNLB) was, thus, performed which revealed a pattern of AFOP. She got an impressive improvement with a long-term therapy of methylprednisolone and low-dose indomethacin, but the shrunken pulmonary lesions persisted throughout the 22-months follow-up visits.

Case Report

A 65-years-old non-smoking female presented with hematochezia for 3 months, and she was diagnosed with rectal adenocarcinoma by colonoscopy and biopsy on September 14th, 2013. She undertook a surgical resection of rectal adenocarcinoma on September 22nd in a tertiary hospital of Hunan Province, China. Before the surgery, she

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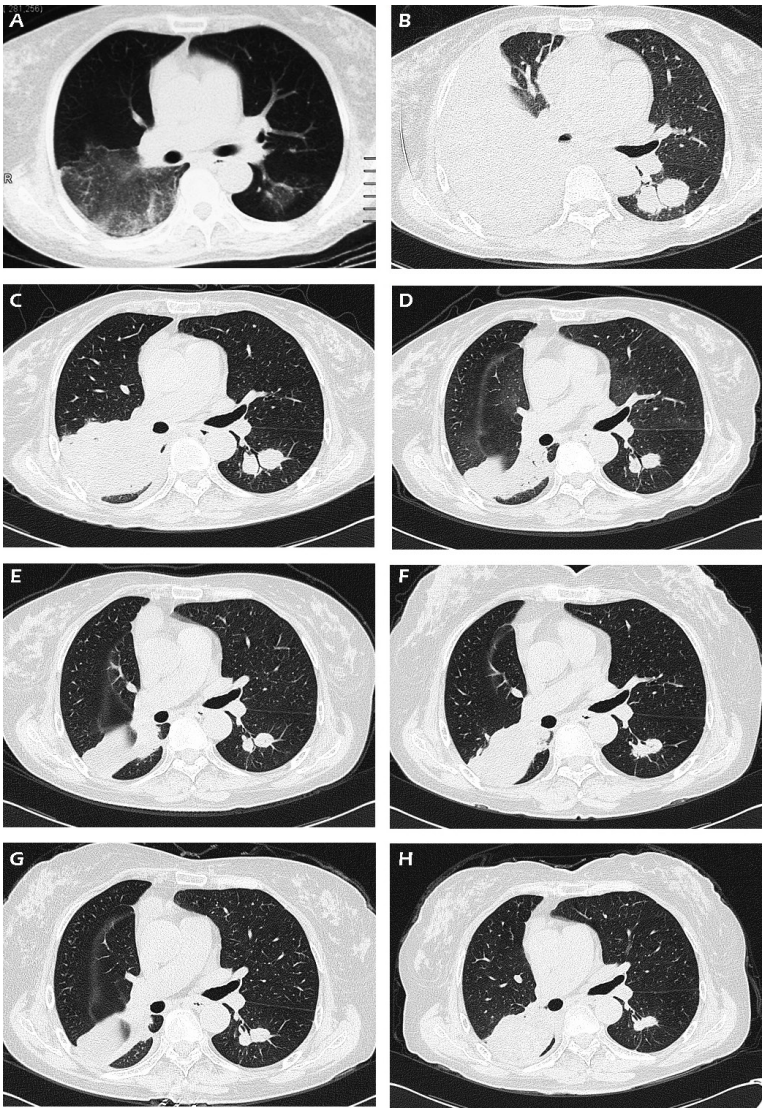

Figure 1. Thoracic computed tomography (CT) scans findings. ***A,*** on the 5th day after surgery, thoracic CT showed bilateral ground glass opacities. ***B,*** on admission to our hospital, thoracic HRCT demonstrated a large consolidation in the right lower lobe and multiple nodules in the left lower lobe. ***C,*** on the 21st day of the steroids treatment (MP 80 mg bid ×5d, MP 40 mg qd×16d, indomethacin 6.25 mg bid×2w), thoracic HRCT showed an obvious resolution (comparing to those on admission). ***D,*** in week 11 of the steroids treatment (MP 80 mg bid ×5d, MP 40 mg qd×6w, MP 20 mg qd×4w, indomethacin 6.25 mg bid×10w), thoracic HRCT showed a small resolution (comparing to those in 21st day). ***E,*** in week 17 of the steroids treatment (MP 80 mg bid ×5d, MP 40 mg qd×6w, MP 20 mg qd×10w, indomethacin 6.25 mg bid×16w), thoracic HRCT showed similar lesions (comparing to those in week 11). ***F,*** in week 25 of the steroids treatment (MP 80 mg bid ×5d, MP 40 mg qd×6w, MP 20 mg qd×10w, MP 16 mg qd×4w, MP 12 mg qd×4w, indomethacin 6.25 mg bid×24w), thoracic HRCT showed similar lesions (comparing to those in week 11). ***G,*** after 3 months of steroids withdrawal, thoracic HRCT showed similar lesions (comparing to those in week 11). ***H,*** after 1 year of steroids withdrawal on June 1st, 2015, thoracic HRCT showed similar lesions (comparing to those in week 11).

was free of fevers or respiratory symptoms and the initial chest X-ray (CXR) revealed no abnormality. On the 5th day after surgery, she developed high fever and cough with purulent sputum. The thoracic computerized tomography (CT) showed bilateral ground glass opacities (Figure 1A). The patient was administered with antibiotics for presumed HAP. A repeat thoracic CT on the 14th day revealed a large consolidation in the right lower lobes and nodules in the left lower lobe. Bronchoalveolar lavage fluid culture was negative. The patient's clinical condition progressively worsened in spite of successive anti infective regimens including carba penem, vancomycin, moxifloxacin, cefoperazone and voriconazole. On the 25th day after surgery, she was transferred to our hospital.

On examination, she was alert and in moderate distress with the following vital signs: temperature 39.4°C, blood pressure 152/90 mmHg, pulse rate 130/min and respiratory rate 26/min. Her oxygen saturation was 94% on 2 L/min oxygen. Palpation of the lungs revealed increased tactile fremitus in the bottom of right lung, consistent with increased breath sound on auscultation. Cardiac examination was notable for a regular tachycardia without murmurs. The rest of her physical examination was unremarkable.

Blood cell analysis testing disclosed a white blood cell count of 14.59×10^9/L with normal neutrophil ratio. The C reactive protein was elevated to 205.00 mg/L. Initial arterial blood gas revealed pH 7.51, PaO_2 65 mmHg, $PaCO_2$ 30 mmHg. Serologic tests for antinuclear antibodies, rheumatoid factors and anti-neutrophil cytoplasmic antibodies were within normal limits. Tuberculin skin test, sputum stains for Acid Fast Bacil-

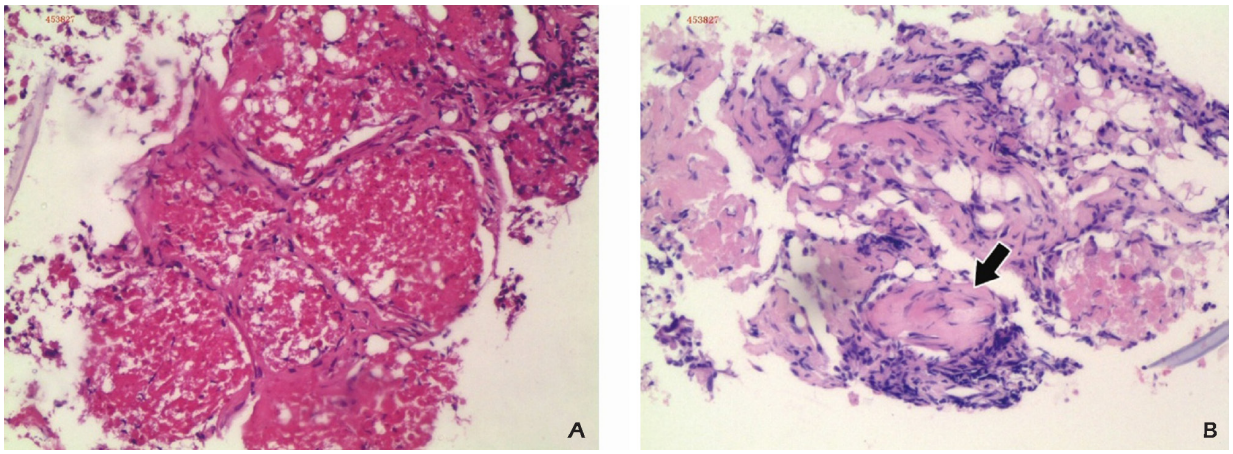

Figure 2. Photomicrographs of the right lower lobe lung tissue. **A,** Prominent fibrin deposit in the form of fibrin "balls" within the alveolar space (Hematoxylin & eosin, original magnifications×100). **B,** Focal intra-alveolar fibroblastic Masson bodies (arrow) are present (Hematoxylin & eosin, original magnifications×100).

li, cultures of blood and sputum were all negative. Thoracic high-resolution CT (HRCT) scan on admission demonstrated further progression of the consolidation and multiple nodules (Figure 1B). CT-guided PNLB was performed with informed consent. The pathologic study of the lung specimens from the right lower lobe demonstrated prominent fibrin depositing in the form of fibrin "balls" within the alveolar space (Figure 2A). Focal organizing pneumonia was present characterized by intra-alveolar fibroblastic Masson bodies (Figure 2B). There were no existence of hyaline membrane, granulomatous inflammation and eosinophilic infiltration. Stains of Alcian blue, Periodic Acid-Schiff and Ziehl-Neelsen were negative. These findings were consistent with AFOP.

With the diagnosis of AFOP, high dose of intravenous methylprednisolone (80 mg every 12 hours) was prescribed for 5 days, leading to a complete relief of symptoms. Then the dose was decreased to 40 mg daily. However, a recurrence of fever and respiratory symptoms appeared 3 days later, which led to an addition of low-dose indometacin (6.25 mg every 12 hours) to the anti-inflammatory therapy since week 2. Soon the symptoms disappeared, and a repeat thoracic HRCT on the 21st day of the steroids treatment showed an obvious resolution (Figure 1C). She was discharged on oral methylprednisolone 40 mg daily in week 7. However, 4 days after discharge, she presented with hematochezia again, which was caused by a rectal anastomotic fistula diagnosed by colonoscopy. The dose of methylprednisolone was decreased to 20 mg daily since Week 8 and the rectum mucosa protecting and nutritional support were enhanced. The hematochezia phased out after 1 week, and the reduction of corticosteroids didn't lead to a relapse in symptoms. Dose of 20 mg daily lasted for 10 weeks, and then was tapered by 4 mg every month. The treatment course of corticosteroids last for 33 weeks. In the week 25 when the methylprednisolone was reduced to 8 mg daily, the indomethacin was discontinued, which last for 24 weeks. Since corticosteroids withdrawal, the follow-up visits have been up to 15 months with no rebound of symptoms, but the abnormalities in the thoracic imaging seemed persistent. Thoracic HRCT scans in week 17 and 25 of corticosteroids treatment, after 3 months and 1 year of steroids withdrawal (Figure 1E-H) showed constant lesions in the original locations similar to those in Week 11 (Figure 1D).

Discussion

A search up to September 1st, 2015 in PubMed and WANFANG DATA was conducted using the search term *acute fibrinous and organizing pneumonia*. A total of non-overlapped 45 individual cases and 4 single-center studies are included in this review. The most common coexisting diseases are infections, connective tissue diseases and hematological diseases. The relevant respiratory symptoms and radiological findings are various and non-diagnostic. Corticosteroids and immunosuppressants are the most common agents prescribed in AFOP. The important information about the clinical characteristics, the treatment and outcome of the reported cases and single-center studies was respectively summarized in Table I[2-40] and Table II[1,41-43].

Table I. Summary of Non-overlapped Cases of Acute Fibrinous and Organizing Pneumonia and the Present Case.

First Author/ Year	Sex, Age	Medical History or Coexisting Disease	Symptoms	Time Evolution	Radiological Findings	Definitive Therapy	Outcome	Follow-up
Kobayashi et al/2005[2]	M, 55Y	Chronic gromerulo-nephritis dialysis	Cough Dyspnea	2 weeks	Diffuse interstitial changes Airspace consolidation	MP 1000 mg/d×3d, Pred 0.5 mg/kg	Improved	3 months
Prahalad et al/2005[3]	M, 14Y	Juvenile dermatomyositis	Dyspnea	4 days	Parenchymal process with patchy densities	MP 1 g/d×3d Cyclosporine Cyclophosphamide	Died of respiratory failure	None
Sverzellati et al/2006[4]	F, 62Y	Hodgkin lymphoma Granulomatous mycosis fungoides	Fever Cough Weakness	NG	Multiple patchy consolidations Nodules with halos of ground-glass attenuation An extensive crazy-paving pattern	Corticosteroid (no details)	Improved	NG
Damas et al/2006[5]	M, 66Y	None	Productive cough Chest pain	2 months	Bilateral consolidations	Pred 1 mg/kg/d for some weeks Cyclophosphamide	Improved	18 months
Cincotta et al/2007[6]	F, 38D	Premature birth (at 30 wks)	Profound hypoxia Bradycardias	NG	Diffuse airspace shadowing	MP 2 mg/kg/d	Die of respira-tory failure	None
Yokogawa et al/2007[7]	F, 52Y	HIV infection Abacavir usage	Dyspnea Productive cough	1 day	Diffuse reticular interstitial infiltrats	Corticosteroid (no details)	Improved	NG
Balduin et al/2007[8]	M, 47Y	Collagen vascular disease	Dry cough Exertional dyspnea	>12 weeks	NG	Steroids and azathio-prine (no details)	Improved	NG
Canessa et al/2008[9]	F, 60Y	Whipple disease	Dyspnea Cough Diarrhea Weight loss	12 weeks	Alveolar consolidation Mild bilateral pleural	Antibiotics	Improved	NG
Tzouvelekis et al/2009[10]	F, 65Y	Osteoporosis Hyperlipidemia	Dry cough Fever Weight loss Breathlessness	1 month	Peripheral and subpleural consolidation	Oral corticosteroid 1 mg/kg	Improved	NG
Vasu et al/2009[11]	M, 64Y	Acute Myelocytic Leukemia Myelodysplastic syndrome Two courses of decitabine	Dry cough Fever	2 weeks	Consolidation	MP 60 mg q6h, Pred 40 mg/d	Improved	NG
Lee et al/2009[12]	M, 60Y	Acute Myelocytic Leukemia Hematopoietic Stem Cell Transplantation Chronic renal failure	Productive cough Dyspnea	3 days	Bilateral diffuse miliary nodules Ground glass opacity Patchy consolidation Right pleural effusioin	MP 60 mg/d, then tapering for 2 months	Died of respiratory failure	None

Continued

Table I. Summary of Non-overlapped Cases of Acute Fibrinous and Organizing Pneumonia and the Present Case.

First Author/ Year	Sex, Age	Medical History or Coexisting Disease	Symptoms	Time Evolution	Radiological Findings	Definitive Therapy	Outcome	Follow-up
Bhatti et al/2009[13]	M, 56Y	Chronic obstructive pulmonary disease Cardiovascular disease Gastroesophageal reflux disease	Dry cough Dyspnea Chest pressure Fever	6 weeks	Bilateral consolidation	MP 1 mg/kg, then tapering Mycophenolate mofetil	Improved	NG
Hariri et al/2010[14]	M, 47Y	Systemic Lupus Erythematosus Secondary antiphospholipid syndrome Large B cell lymphoma	Exertional dyspnea Productive cough	3-4 weeks	Segmental and subsegmental pulmonary emboli Consolidations with air bronchograms	Pred 60 mg/d Cyclophosphamide	Improved	NG
Heo et al/2010[15]	M, 40Y	HIV infection	Dry cough Exertional dyspnea	3 months	Diffuse ground-glass opacities Consolidation Ill-defined nodular infiltration	Pred 1 mg/kg/d × 4 weeks, then tapering for 8 months	Improved	>8 weeks
Santos et al/2010[16]	M, 44Y	Hepatitis C	Chest pain Hemoptysis	4 weeks	Opacities Diffuse hazeiness Nodular lesion	Surgery	Improved	NG
Zhang et al/2010[17]	M, 73Y	Atrial fibrillation Amiodarone use	Fever Cough Dyspnea Purpura	3 days	Patchy opacities Nodules with air bronchogram	MP 80 mg/d × 3 days, MP 40 mg/d × 5 days, MP 24 mg/d	Improved	NG
Ribera et al/2011[18]	F, 69Y	Hypertension Diabetes mellitus Chronic liver disease	Arthro-myalgias Rhinorrhea Dry cough Fever Shortness of breath	4 days	Consolidation Ground-glass opacities	Corticosteroid (no details)	Died of ARDS and MODS	None
Rapaka et al/2011[19]	M, 38Y	HIV infection HBV infection	Cough Fever Shortness of breath	1 week	Ground-glass opacities Ill-defined nodular infiltration Consolidation	Systematic corticosteroid (no details for initial dosage), followed by pred 40 mg/d for 3 months	Improved	3 months
Mittal et al/2011[20]	F, 14Y	None	Fever Dry cough Breathlessness Pleuritic chest pain	1 week	Complete consolidation Pleural effusion Bronchopneumonia	Pred 40 mg/d, then tapering for 1 month	Improved	1 month
Merrill et al/2011[21]	F, 53Y	Hypertension Fibromyalgia Myelodysplastic syndrome	Chest pain Dry cough Dyspnea Weight loss	4 months	Enlarged mediastinal and hilar lymph nodes Scattered ground-glass linear Nodular opacities	Solumedrol 100 mg/d, then tapering Increasing the dose in the relapse	Died of bone marrow failure	None

Continued

Table I. Summary of Non-overlapped Cases of Acute Fibrinous and Organizing Pneumonia and the Present Case.

First Author/ Year	Sex, Age	Medical History or Coexisting Disease	Symptoms	Time Evolution	Radiological Findings	Definitive Therapy	Outcome	Follow-up
Hariri et al/2012[22]	F, 55Y	Cleaning flooded basement and car	Cough Shortness of breath Fever Chills Fatigue	1 week	Multifocal consolidation Patchy ground glass opacities	Corticosteroid (no details)	Improved	NG
Hariri et al/2012[22]	F, 45Y	Exposure of leaky roof	Cough Shortness of breath Fever Chills Fatigue	NG	Bilateral pneumonia	Corticosteroid (no details)	Improved	NG
Valim et al/2012[23]	F, 39Y	Undifferentiated connective tissue diseases	Cough Dyspnea Fever Dyspnea	8 months	Intersitial infiltrates with ground glass opacities Foci of parechymal densification Small calcified nodules	MP 1 g/d ×3 days Cyclophosphamide 1 g/d × 3 days	Died of pulmonary hemorrhage	None
Lopez-Cuenca et al/2012[24]	F, 27Y	Marden-Walker syndrome Permanent tracheostomy	Fever Shortness of breath	2 days	Diffuse infiltrates	No treatment after biopsy	Died of MODS	None
Guimaraes et al/2012[25]	F, 55Y	Hypothyroidism Primary biliary cirrhosis	Dyspnea Fatigue Dry cough Thoracic pain Haemoptysis	1 month	Peribronchial opacities Ground glass opacities Reversed halo sign	Pred 1 mg/kg/d, then tapering	Improved	14 months
Gui et al/2012[26]	M, 48Y	None	Fever Cough Dyspnea	2 months	Multiple patchy subpleural consolidations	MP 40 mg bid × 5 days, then tapering	Improved	None
Gui et al/2012[26]	M, 43Y	Myelodysplastic syndrome	Fever Chest pain	2 weeks	Consolidation	MP 240 mg/ d × 3 d, MP 120 mg/d × 7 d, then tapering Increasing the dose in the relapse	Died of relapse	None
Labarinas et al/2013[27]	M, 10Y	Very severe aplastic anemia Hepatic failure Dyskeratosis congenita	Fever Respiratory symptoms Pleural pain	1 month	Pulmonary nodules Bibasal condensations Bilateral pleural effusion	Corticosteroids (no details) Cyclosporin Antithymocyte globulin	Improved	16 months
Otto et al/2013[28]	F, 66Y	End-stage pulmonary fibrosis Double sided lung transplantation	Cough Respiratory failure	1 month	Diffuse pulmonary infiltrates Ground glass opacities Bronchiectasis Consolidation	Corticosteroid (no details)	Died of respratory failure	None

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Table I. Summary of Non-overlapped Cases of Acute Fibrinous and Organizing Pneumonia and the Present Case.

First Author/ Year	Sex, Age	Medical History or Coexisting Disease	Symptoms	Time Evolution	Radiological Findings	Definitive Therapy	Outcome	Follow-up
Qiu et al/2013[29]	M, 43Y	Myelodysplastic syndrome	Fever Chest pain	2 weeks	Consolidation Slight pleural effusion	MP 160 mg/d×5d, MP 80 mg/d×5d, MP 40 mg/d × 1 month	Improved	1 month
Qiu et al/2013[29]	F, 65Y	None	Productive cough Exertional dyspnea	5 days	Diffuse consolidations	MP 160 mg/d×7d, MP 80 mg/d×5d, Pred 40 mg/d, then tapering	Improved	2 months
Qiu et al/2013[29]	F, 61Y	Asthma Hypertension Diabetes mellitus	Cough Dyspnea	2 months	Consolidation Patchy ground-glass opacities	MP 80 mg bid×5d, MP 40 mg bid×5d, Pred 40 mg/d	Improved	1 month
Qiu et al/2013[29]	F, 52Y	None	Fever Productive cough	20 days	Patchy ground glass opacities	MP 80 mg/d×7d, MP 40 mg/d×5d, Pred 40 mg/d × 1 month	Improved	1 month
Qiu et al/2013[29]	M, 52Y	Hypertension Asthma	Fever Cough Chest tightness Shortness of breath	20 days	Consolidation	MP 80 mg/d×7d MP 40 mg/d×5d, Pred 40 mg/d, then tapering	Improved	3 months
Al-Khouzaie et al/2013[30]	M, 45Y	None	Malaise Arthralgia Chest pain Dyspnea Dry cough	8 weeks	Patchy peripheral consolidations	MP 60 mg q6h, Pred 50 mg/d	Improved	>3 months
Sauter et al/2014[31]	F, 66Y	Anti-synthetase syndrome	Pruritic rash Muscle aches Productive cough Dry cough	NG	Patchy peripheral airspace consolidation	Corticosteroid (no details) for 2 years	Improved	2 years
Lococo et al/2014[32]	F, 65Y	None	Dyspnea	NG	Multiple bilateral consolidation	Corticosteroid (no details)	Improved	6 weeks
Xu et al/2014[33]	M, 63Y	None	Dyspnea Fever	20 days	Pneumonia-like change (no details)	MP 80 mg bid ×3 days, MP 40 mg bid ×1 week, MP 40 mg qd ×1 week, MP 20 mg bid × 4 months, MP 20 mg qd	Improved	5 months

Continued

Table I. Summary of Non-overlapped Cases of Acute Fibrinous and Organizing Pneumonia and the Present Case.

First Author/ Year	Sex, Age	Medical History or Coexisting Disease	Symptoms	Time Evolution	Radiological Findings	Definitive Therapy	Outcome	Follow-up
Matsuo et al/2014[34]	M, 90Y	Brain infarction Diabetes mellitus	Gait disturbence	NG	Bilateral infiltration	NG	Died (no detalis)	None
Akhtar et al/2015[35]	F, 68Y	Diabetes mellitus Spinal stenosis Upper respiratory tract infection	Shortness of breath High fever Productive cough	2 weeks	Soft tissue nodular infiltrates Dense consolidation Ground glass opacification and haze Atelactatic changes Pleural thickening Calcified pleural plaques	MP 60 mg/kg q6h, Pred 40 mg/d, then tapering	Improved	4 months
Alici et al/2015[36]	F, 48Y	Double lung transplantation	Fever	1 day	Consolidation	MP 1 g/d × 3 days, Pred 1 mg/kg/d	Improved	12 months
Renaud-Picarda et al/2015[37]	M, 22Y	Bilateral lung transplantation Cervicolateral adenopathy	Shortness of breath Loss of appetite	NG	Ground-glass opacities Fine-mesh reticulations Bronchiectasis by traction	Retransplantation of lungs	Improved	24 months
Garcia et al/2015[38]	M, 46Y	None	Dyspnea Cough Night sweats Fever	4 days	Bilateral diffuse miliary nodules Subpleural consolidations Hilar and mediastinal adenopathy	MP (no details)	Improved	NG
Piciucchi et al/2015[39]	M, 79Y	Pulmonary asbestos-related lesions Amiodarone usage	Dyspnea Dry cough Low-grade fever	NG	Pleural effusion Ground glass attenuation Hemithorax volume reduced	MP 40 mg twice a day Withdrawl of amiodarone	Improved	NG
Hara et al/2015[40]	M,70Y	None	Fever Dry cough Tachypnea	1 week	Air space consolidation Ground glass opacity	MP 1 g/day × 3 days, Pred 0.5 mg/kg	Improved	NG
Zhou et al/2015	F, 65Y	Rectal adenocarcinoma Surgical resection	Fever Productive cough	25 days	Ground glass opacity Consolidation Multiple nodules	MP 80 mg twice a day ×5 days, MP 40 mg/d ×6 weeks, MP 20 mg/d ×10 weeks MP 16 mg/d ×4 weeks, MP 12 mg/d ×4 weeks, MP 8 mg/d × 4 weeks, MP 8 mg every other day× 4 weeks, then withdrawl Indometacin 6.25 mg bid for the first 6 months	Improved	22 months

F, female; M, male; Y, year-old; D, day-old; MP, methylprednisolone; Pred, prednisone; NG, not given; ARDS, acute respiratory distress syndrome; MODS, multiple organ dysfunction syndrome. The last case presented above is our case.

Table II. Summary of reported single-center studies of acute fibrinous and organizing pneumonia.

First Author/ Year	Patients	Possible Associated Clinical Conditions	Symptoms	Radiological Findings	Outcome
Beasley et al/2002[1]	N=17 10 males 7 females Average age 62 years	Definitive or probable collagen vascular disease (3), Amiodarone (1), Sputum culture positive for Haemophilus influenzae (1), Lung culture positive for Acinetobacter sp. (1), Lymphoma (1), Hairspray (1), Construction work (1), Coal mining (1), Zoological work(1)	Dyspnea (11), Fever (6), Cough (3), Hemoptysis(2)	Bilateral basilar infiltrates(4), Bilateral diffuse infiltrates greater in lower lobes(1), Bilateral airspace disease(2), Bilateral reticulonodular infiltrates(1), Diffuse patchy infiltrates(1), Infiltrates(2), Consistent with atypical pneumonia(1), Consistent with pulmonary edema(1), Consistent with interstitial pneumonia(1), A diffuse infiltrate in the right lung(1), NG(2)	Died of disease(9), Improved(7), Died of other causes(1)
Hwang et al/2005[41]	N=6 No details about gender or ages	SARS-CoV positive(6)	NG	NG	Died of disease(6)
Paraskeva et al/2013[42]	N=22 No details about gender or ages	Lung transplantation(22)	NG	Bilateral infiltrates, Ground-glass change, Thickening intralobular septal	Died of disease(21)
Feinstein et al/2015[43]	N=10 4 males 6 females Average age 59.6 years	Cancer (10), Active cancer (5), Prior radiation (6), Prior chemotherapy (8)	Cough(5), Dyspnea(4), Wheezing(2), Fatigue(2), Fever(3), Respiratory failure(2)	Nodule or mass (7), Consolidation(5), Ground-glass (2), Air bronchograms (5), Mediastinal adenopathy(2), Pleural effusion (2), Cavitation (1), Reverse halo sign (1), Bronchiectasis (2), Fibrosis (1)	Died of other couses (4)

N, number of patients; SARS-CoV, SARS –coronavirus; NG, not given. The numbers enclosed in parentheses are the numbers of patients.

AFOP was classified as a rare histologic pattern of idiopathic interstitial pneumonias (IIPs) rather than a distinct form in the latest international classification of IIPs released by the American Thoracic Society and the European Respiratory Society in 2013[44], because the published evidence was insufficient to warrant recognition as a specific entity. Beasley et al[1] believed that AFOP was a variant of DAD based on the similar mortality. However, given the significant overlap of pathological components between OP and AFOP, Feinstein et al[43] regarded AFOP as a fibrinous variant of OP with a worse prognosis.

AFOP is reported in associated with a wide spectrum of clinical conditions. Although numerous conditions are reported, quite a few cases are idiopathic, and the pathogenesis of AFOP remains unclear. Some researchers[18,28] speculate that AFOP may be a pulmonary manifestation of an immune dysregulation syndrome. As more and more microorganisms are confirmed in AFOP, the role of infection cannot be unheeded. One probable interpretation on pathogenesis is that the abnormal immune system, which is activated by infection, attacks the host. In the present case, the acute symptoms and the abnormalities in thoracic radiographic findings emerged rapidly after the surgery, and the antibiotics and antifungal drugs did not result in symptomatic or thoracic imaging relief. Therefore, though lacking of confirmed viral organisms, the viral infection after the surgery may be an "activator" of the complicated pathogenesis of AFOP. Since the abnormalities in thoracic imaging emerged within a week after the resection of the original tumor, and the pathological findings didn't show malignant cellular proliferation, the likelihood of pulmonary metastasis was tiny. What's more, the favorable outcome and the follow-up visits also exclude the diagnosis of pulmonary metastasis.

The most successful agents on AFOP are corticosteroids. Regimens of 0.5-1 mg/kg/d of prednisone (or equivalent) are usually prescribed initially. Sometimes a pulse therapy of corticosteroids is administered in some fulminant cases[2,26,36,38]. There is no consensus on treatment courses so far. Besides the corticosteroids, immunosuppressive agents have been tried on AFOP, including cyclophosphamide, mycophenolate mofetil, cyclosporine and azathioprine. Most patients administered with immunosuppressive agents are coexistent with connective tissue diseases[3,14,26,33]. Lung retransplantation was reported[40] as a successful cure in a patient experiencing AFOP following lung transplantation. While the necessity of anti infective agents in AFOP is not acknowledged by most researchers, it's unreasonable to obliterate its role in the whole treatment. Actually, most patients had been administered with a sufficient anti infective therapy before confirming the pathologic pattern.

In the present case, the agents and their dosages were individualized according to the patient's condition, the radiological evolution and the side effects. As the most successful agent on AFOP, corticosteroids were prescribed as soon as confirming the diagnosis. The initial dose (80 mg every 12 hours) was fairly high to arrest and reverse the fulminant disease. And when the agents took effect, the maintaining dose was decreased directly to 40 mg daily to avoid the severe side effects of high-dose corticosteroids. However, the original symptoms were onset again soon, which meant the dose used was not potent to control the inflammation. In this case, indomethacin was added to avoid resuming high-dose corticosteroids, and it was the first time that a long-term non-steroidal anti-inflammatory drug (NSAID) was administrated to AFOP. The favorable response indicated that the indomethacin had a synergistic or additive effect against AFOP when combined with corticosteroids. There are two reasons why a NSAID rather than an immunosuppressive agent was added. On one hand, NSAIDs have a much quicker therapeutic effect than the latter, which were preferred to be prescribed in an acute phase. On the other hand, it is verified that the NSAIDs have anticolorectal cancer activity[45,46], while the potent immunosuppressive activity of the latter is unfavorable for a patient with a malignant tumor. As for the rectal anastomotic fistula, we believe the prior surgery and the corticosteroids are the main contributing factors. Though it is widely accepted that NSAIDs have a high risk of serious gastrointestinal side effects, indomethacin contributed little to the fistula, for the dose prescribed in our patient was much lower than the conventional dose. Given that the patient's healthy condition was unstable at that time, the conservative treatment might be superior to the surgery. When the dose of methylprednisolone was decreased to 20 mg daily, the patient's condition remained stable, indicating that the lower dose corticosteroids plus indomethacin could probably control the inflammation. Nonetheless, the sizes of lesions seemed fixed since the last 6 weeks treatment of methylprednisolone 20 mg daily, so whether this dosage was really powerful for our patient was

in doubt. Even looking back now, it is difficult to determine the optimal maintaining dose of corticosteroids in our case. However, after weighing the possibility of complete resolution of lesions against the potential systemic side effects of a prolonged, high-dose corticosteroids treatment, we believed that the complete resolution was neither the prerequisite of drug withdrawal, nor the prerequisite of treatment success. Since the initial timing of effective treatment was much later than other cases, the persistent lesion might have transformed to other unresolved pathological patterns.

The prognosis of AFOP is unfavorable as a whole. There are a few identifiable clinical or histologic parameters associated with the outcome. Beasley et al[1] considered that AFOP might have 2 distinct patterns of disease progression and outcome, the acute clinical course and the subacute one, and the need for mechanical ventilation was correlated with a poor prognosis. An updated research found that the over expression of hemeoxygenase-1 in the lungs might influence the pathophysiology and clinical outcomes of subacute AFOP[38]. Patients sometimes suffer from the relapse for the discontinuation[12] or improper tapering[18]. The relapse will prolong the length of hospital stay and the treatment course, and then increase the risk of infection and adverse reactions, but don't always lead to a poor outcome[12].

Conclusions

We report a case of AFOP who was misdiagnosed as HAP after a surgical resection of rectal adenocarcinoma. She was successfully treated with long-term corticosteroids and low-dose indomethacin. This case highlights the importance of this uncommon pattern of acute lung injury in the differential diagnosis of the presumed pulmonary infection with an unfavorable therapeutic effect. The immune system activated by infection may play a vital role in the pathogenesis of AFOP. Low-dose indomethacin combined with corticosteroids may be a new choice for AFOP treatment. More studies are warranted regarding the pathogenesis and treatment of AFOP.

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Conflicts of interest

The authors declare that they have no conflict of interests.

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