# Increased neutrophils and IL-17A in a rare organizing pneumonia secondary to extrapulmonary operation

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**Abstract:** Organizing pneumonia (OP) is a clinical syndrome caused by various diseases. The most common causes are infection, connective tissue disease, radiation therapy, drug reaction and thoracic operation. Herein, we describe the case of a patient that developed OP after fracture internal fixation. The case was confirmed to be OP by computer tomographic (CT)-guided percutaneous needle lung biopsy, and other causes of OP were excluded. After the initiation of corticosteroid therapy, marked clinical and radiographic improvements occurred. In addition, we discovered increased neutrophils and IL-17A in the lung tissue of the patient. To the best of our knowledge, this is the first case report about OP secondary to extrapulmonary operation.

**Keywords:** Organizing pneumonia (OP); extrapulmonary operation; neutrophils; IL-17A

## Introduction

Organizing pneumonia (OP), which used to be called bronchiolitis obliterans organizing pneumonia (BOOP), was first described as a clinical pathology syndrome characterized by granulation tissue in the lumens of small airways, alveolar ducts and the alveolar space by Epler *et al.* in 1985 (1). This condition is regarded as a common reaction of lung tissue to different injury factors and a mutual manifestation of a variety of diseases in the lungs rather than an independent disease. When the lung is injured by various acute and chronic factors, it can be manifested as diffuse alveolar damage, OP, acute fibrinous and OP and certain types of fibrotic lung disease (2) In 2001, the American Thoracic Society and the European Respiratory Society (ATS/ERS) referred to idiopathic OP as cryptogenic pneumonia (COP), which is recognized as a subtype of idiopathic interstitial pneumonia and OP with specific etiology as secondary organizing pneumonia (SOP) (3). As we know, a number of diseases and factors are correlated with OP, such as infection (4), connective tissue disease (CTD) (5,6), radiation therapy (7), drug reaction (8), cancer (9), hematological diseases (10), inflammatory bowel disease (11), organ transplantation (12), gastroesophageal reflux disease (13), toxic exposure (14), thyroid disease (15), and menstruation (16). In recent years, some cases of OP following chest surgery have also been reported (17). A case of acute fibrinous and OP after a surgical resection of rectal adenocarcinomas has recently been reported (18), which could still not prelude the effects of cancer. However, as far as we know, until now, no cases of OP secondary to nonthoracic surgery have been reported. Here, we report a
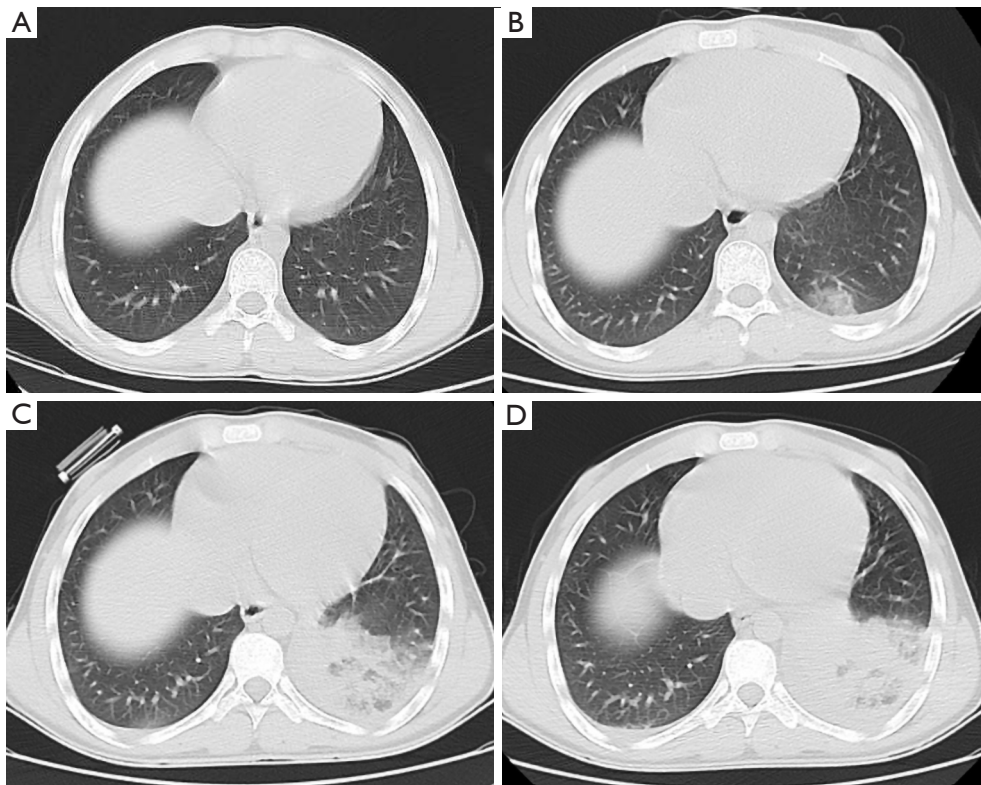
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**Figure 1** Changes in CT signs over the course of the disease in the patient. (A) No significant changes in the two lungs before the operation; (B) clustered and patchy shadows in the lower lobes of bilateral lungs after the operation; (C) bilateral lower pulmonary infection with consolidative opacities in the left lower lung zones and left pleural effusion after the anti-infection treatment; (D) bilateral lower pulmonary infection with bilateral pleural effusion (especially the left lung), 3 days after *Figure 1C*. CT, computer tomographic.

case of OP secondary to internal fixation surgery for a left clavicular fracture.

## Case presentation

A previously healthy 19-year-old patient was transferred to our hospital from the outer court with a 9-day history of fever, cough and expectoration in September, 2015. The patient experienced an internal fixation surgery for a left clavicular fracture 8 days before the outset of the symptoms. No obvious abnormalities were observed in the chest computer tomographic (CT) (*Figure 1A*) before the operation, and ceftizoxime was used to prevent infection after surgery. After the operation, the chest CT showed cluster and patchy shadows in the lower lobes of the bilateral lungs, but no pleural effusion was observed in either lung (*Figure 1B*). At first, the condition was considered a postoperative pulmonary infection, and a variety of antibiotics, including piperacillin-tazobactam,

moxifloxacin, vancomycin, imipenem and linezolid, were successively given to the patient. Nevertheless, despite treatment with antibiotics and supportive drugs, the patient still continued to deteriorate (*Figure 1C,D*). Therefore, he was transferred to our hospital for further diagnosis and treatment. He did not have any chronic diseases except a history of chronic sickle cell anemia for more than 10 years. In addition, he did not have a history of smoking, alcohol consumption and specific medication or an exposure history to industrial toxicant, hazardous dust and radiation.

Physical examination revealed the patient had a temperature of 38.5 ℃ a heart rate of 115 beats/min, a respiratory rate of 20 breaths/min, a blood pressure of 120/80 mmHg and an oxygen saturation level of 95%. Lung examination showed tactile fremitus of the left lung was weakening, percussion of lower left lung was voiced, breathing of the left lower lung was low, breathing of the right lung was thick, and moist rale was heard in both of the lower pulmonary regions. Laboratory data suggested a white
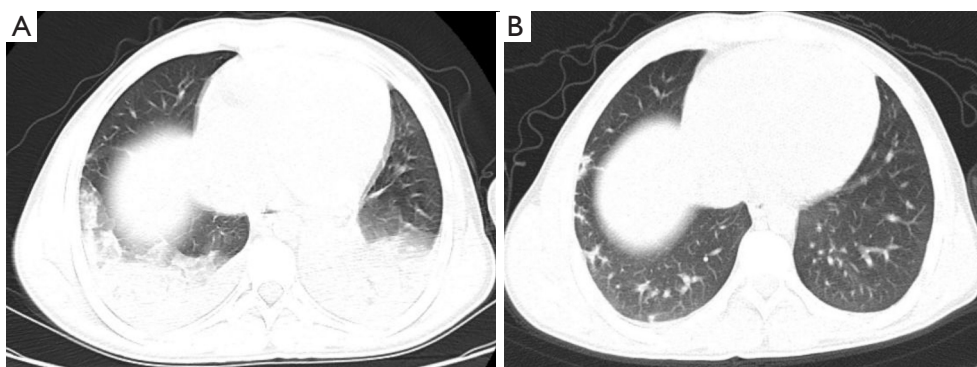
**Figure 2** Changes in CT signs over the course of disease in the patient. (A) Bilateral lower pulmonary inflammatory changes and bilateral pleural effusion; (B) repeat CT scan of chest after treatment with glucocorticoids for 6 weeks with significant improvement of parenchymal changes. CT, computer tomographic.
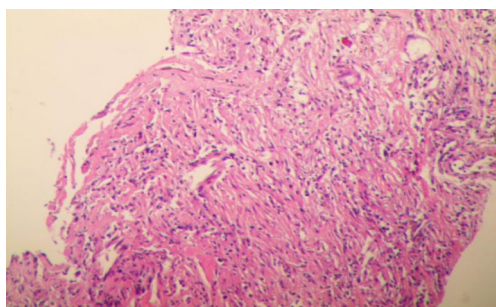


**Figure 3** Histopathological changes in the patient. Organization and polypoid granulation tissue within small bronchioles, alveolar ducts and alveoli and a larger number of inflammatory cells infiltrated into lung interstitial tissue. (Hematoxylin and eosin staining, ×200).

blood cell count of 10,720 cells·mm$^{-3}$ (10.72 cells ×10$^9$ L$^{-1}$) with 62.8% neutrophils, an erythrocyte sedimentation rate (ESR) of 93 mm/h and a C-reactive protein (CRP) level of 121 mg/L. Pleural effusion examination indicated extravasate. However, the etiological examination including bacteria, fungus and tubercule bacillus were all negative. In addition, the antinuclear antibody and antineutrophil cytoplasmic antibody counts were all negative, and the fiberoptic bronchoscopy examination showed no obvious abnormality.

Initially, we considered the patient to be afflicted with hospital-acquired pneumonia. Therefore, we gave the patient a variety of broad-spectrum antibacterial agents, but the patient's symptoms still did not improve after anti-infective treatment, and the lesion in chest CT was still progressing (*Figure 2*). Combined with the patient's history,

symptoms, auxiliary examinations and the response to drugs, we considered the possibility of OP. Therefore, a CT-guided percutaneous needle lung biopsy was performed on the patient, and the patient received an empirical therapy of 40 mg methylprednisolone per day according to our experience. The pathological findings showed interstitial fibrosis hyperplasia and a larger number of inflammatory cells infiltrated into lung interstitial tissue (*Figure 3*), which confirmed OP. His respiratory symptoms improved gradually, and his temperature gradually returned to normal after treatment with methylprednisolone for a week. A reexamination of CRP was 3.28 mg/L. He was discharged one day later and continued taking 20 mg prednisone acetate daily. After the patient was discharged from hospital, 36 days later, all symptoms disappeared, and a significant improvement in the chest CT was seen (*Figure 2B*). Therefore, the dose of prednisone acetate was reduced to 15 mg per day. Three months later, the dose of prednisone acetate was decreased to 10 mg for maintenance therapy. We have been following up with the patient, and no relapse was observed until now.

To further confirm the pathogenesis of OP secondary to extrapulmonary operation, we further analyzed hematoxylin and eosin (HE)-staining, alkaline phosphatase (ALP)-staining and immunohistochemical staining of pulmonary tissue slices of the patient compared with control subject after receiving the consent of the subjects. Our case also revealed that pulmonary inflammation was evident in the patient with organic pneumonia (*Figure 4*). Moreover, neutrophils in lung tissue of the patient were also increased (*Figure 5*). IL-17A is an important inflammatory cytokine that is closely associated with Th17 cell inflammation. To
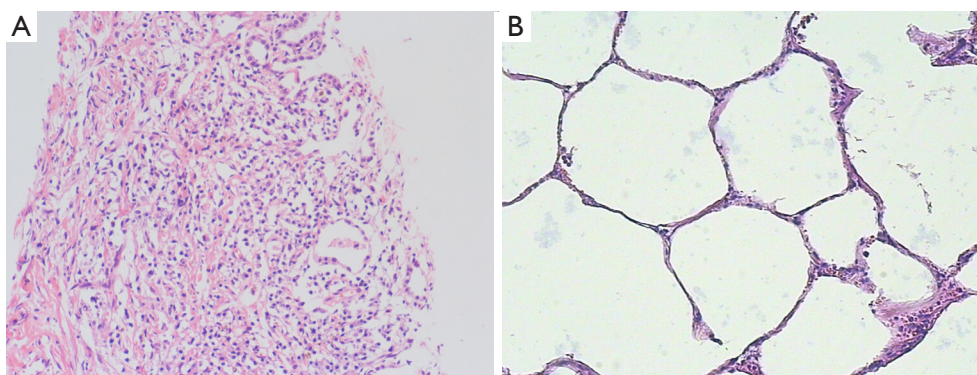
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**Figure 4** HE-staining in the patient and a healthy control. (A) HE-staining of the patient: lymphocytes increased in the lung tissue compared with the healthy control; (B) HE-staining of the healthy subject. (HE-staining, ×200). HE, hematoxylin and eosin.
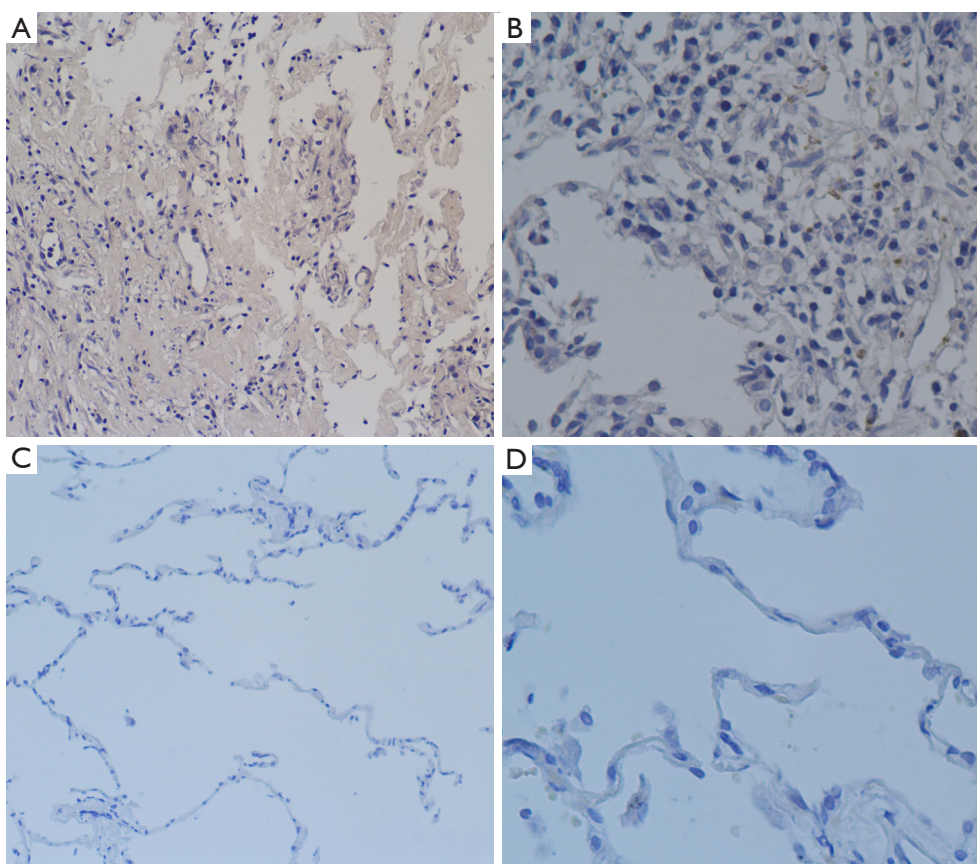


**Figure 5** ALP-staining of the patient and a healthy control. (A) ALP-staining of the patient: neutrophils increased slightly in the lung tissue compared with the healthy control (ALP-staining, ×200); (B) ALP-staining of the patient: neutrophils increased slightly in the lung tissue compared with the healthy control (ALP-staining, ×400); (C) ALP-staining of the healthy subject (ALP-staining, ×200); (D) ALP-staining of the healthy subject (ALP-staining, ×400). ALP, alkaline phosphatase.
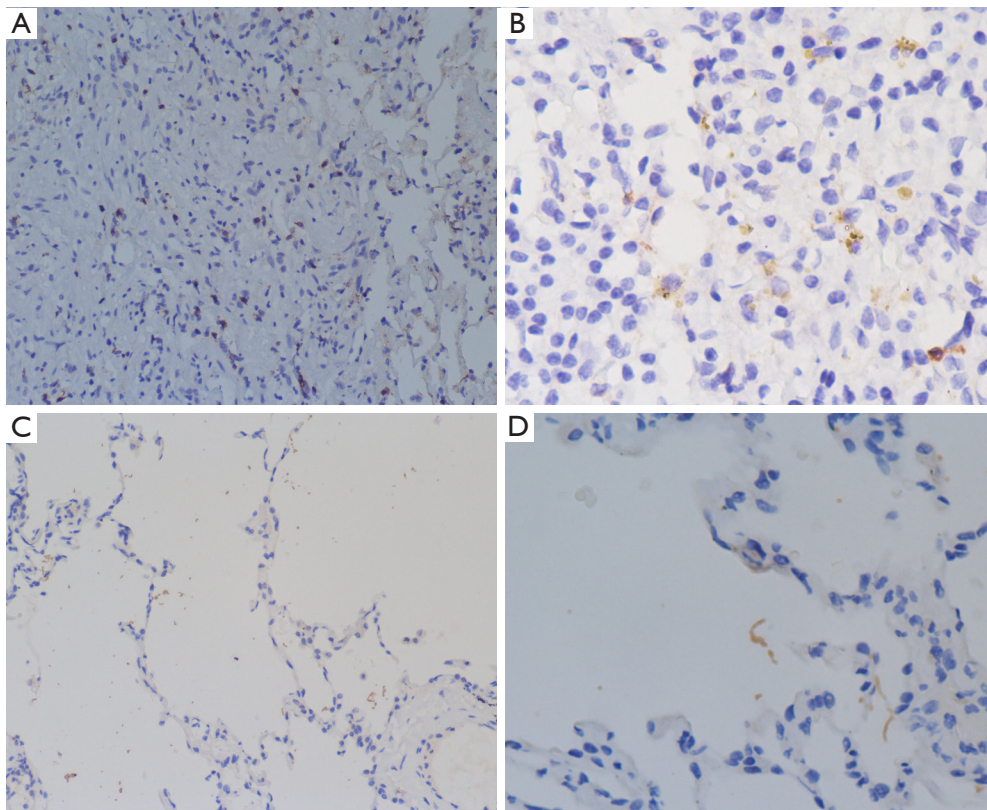
**Figure 6** Immunohistochemical staining of the patient and a healthy control. (A) Immunohistochemical staining of the patient: the positive expression of IL-17A was more than that of the healthy subject (immunohistochemical staining, ×200); (B) immunohistochemical staining of the patient: the positive expression of IL-17A was more than that of the healthy subject (immunohistochemical staining, ×400); (C) immunohistochemical staining of the healthy subject (immunohistochemical staining, ×200); (D) immunohistochemical staining of the healthy subject (immunohistochemical staining, ×400).

further verify that whether Th17 cells were involved in the development of OP, we performed an immunohistochemical staining analysis of IL-17A. Consequently, we found positive expression of IL-17A in the patient was increased (*Figure 6*). Consequently, we hypothesized that neutrophils and Th17 cells may be involved in the pathogenesis of OP.

## Discussion

Many noninfectious processes, especially OP, are easily and mistakenly diagnosed as hospital acquired pneumonia. To date, the pathogenesis of OP is still not completely understood. Some scholars consider that alveolar epithelial cells and microvascular endothelial cells are damaged by multifarious factors, which start the repair mechanism of the body, promoting alveolar macrophages to produce abundant proinflammatory cytokines and chemokines, including interleukin 1 beta (IL-1β), IL-6, IL-8, tumor necrosis factor alpha (TNF-α) and CC chemokine ligand 18 (CCL18) (19). At the same time, the activation of macrophages and lymphocytes also enlarges the Th1 response, which further promotes the growth of granulation tissue and the infiltration of chronic inflammation cells in the pulmonary interstitium (20). Because of the injury of alveolar epithelial cells and microvascular endothelial cells, which damages the integrity of the alveolar wells, the newborn granulation tissue grows to the alveoli and alveolar ducts and other small airways, forming the OP. Recently, Shokri *et al*. revealed that an LPS-responsive beige-like anchor gene mutation may participate in the pathogenesis of OP (21). Bronchoalveolar lavage fluid (BALF) analysis of OP patients revealed a significant increase in the proportion of lymphocytes, neutrophils, eosinophils and mast cells and a significant decrease in the percentage of macrophages (22).

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This report described one patient with OP attributed to internal fixation surgery for a left clavicular fracture. The patient had no symptoms, and the chest CT was normal before the operation, but the patient developed a fever, cough, expectoration and multiple patchy exudations in the chest CT postoperation. At first, we considered the diagnosis of hospital acquired pneumonia and gave the patient powerful anti-infective therapy, but no improvement was observed in clinical conditions and chest radiograph. Combined with patient's history, symptoms, laboratory examination and imagological examination, diagnosis and treatment process and response to drugs, we examined the possibility of a noninfectious disease, and CT-guided lung biopsy confirmed OP. Significant clinical and radiographic improvements were seen after initiation of corticosteroid therapy, which further confirmed the diagnosis of OP. In addition, no other causes of OP were observed in the patient. Therefore, the diagnosis of OP secondary to fracture internal fixation surgery was clear.

We have not found any reported cases of OP after fracture internal fixation surgery and other nonthoracic surgery. Therefore, this should be the first case report about an unusual OP secondary to extrapulmonary operation. In addition, this study suggests that neutrophils and IL-17A may be involved in the pathogenesis of OP. The case implied that extrapulmonary surgery may also be an important cause of OP. When a patient has a cough, fever and other symptoms after nonthoracic operation and repeated antibiotic treatment is ineffective, we should be cautious of the occurrence of OP.

## Acknowledgments

## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* The written informed consent was obtained from all subjects, and this study was approved by the Ethics Committee of the First Affiliated Hospital of Nanjing Medical University.

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