

## Original Article

# Nonspecific interstitial pneumonia overlaps organizing pneumonia in lung-dominant connective tissue disease

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**Abstract:** Here, we reported two cases of nonspecific interstitial pneumonia overlap organizing pneumonia (NSIP/OP) with lung-dominant connective tissue disease (LD-ILD). The first case is a patient with hands of chapped skin, right-sided pleuritic chest discomfort, weakness, positive ANA and antibodies to Ro/SS-A (+++) and Ro-52 (++) . In the second case, there were Reynaud's disease, and nucleolus-ANA increased (1:800). Chest high resolution CT scan in both cases showed ground-glass opacifications, predominantly in basal and subpleural region and the pathologic manifestation were correlated with NSIP/OP, which were previously discovered in Sjogren syndrome, PM/DM and other rheumatic diseases. The two cases of NSIP/OP with LD-CTD we reported expand disease spectrum of NSIP/OP pathologic types in ILD. However, it is necessary to process large-scale studies.

**Keywords:** Nonspecific interstitial pneumonia, organizing pneumonia, lung-dominant connective tissue disease

## Introduction

Connective tissue disorders (CTDs) are a heterogeneous group of autoimmune disorders, which is shown difference manifestations, including interstitial disease, airway disease, pleural lesions, and vascular disease. Interstitial lung diseases are a common symptom of CTDs. About 15% of patients evaluated as interstitial lung diseases (ILD) are considered as patients with potential CTDs [1]. Therefore, in some of these patients, the lung disease may precede the clinical symptoms of CTDs [2]. ILD associated with CTDs are most commonly in the nonspecific interstitial pneumonia (NSIP) and the usual interstitial pneumonia (UIP). Organizing pneumonia usually associate with other histologic patterns of interstitial pneumonia in CTDs. NSIP overlapped OP (NSIP/OP) histological pattern was mostly discovered in Sjogren syndrome, PM/DM and other rheumatic diseases. According to criteria of lung-dominant CTD (LD-CTD) proposed by Fischer A et al., the symptoms of these patients do not meet strict criteria of a certain CTD according to current rheumatologic classification systems [3]. To better know the disease spectrum of

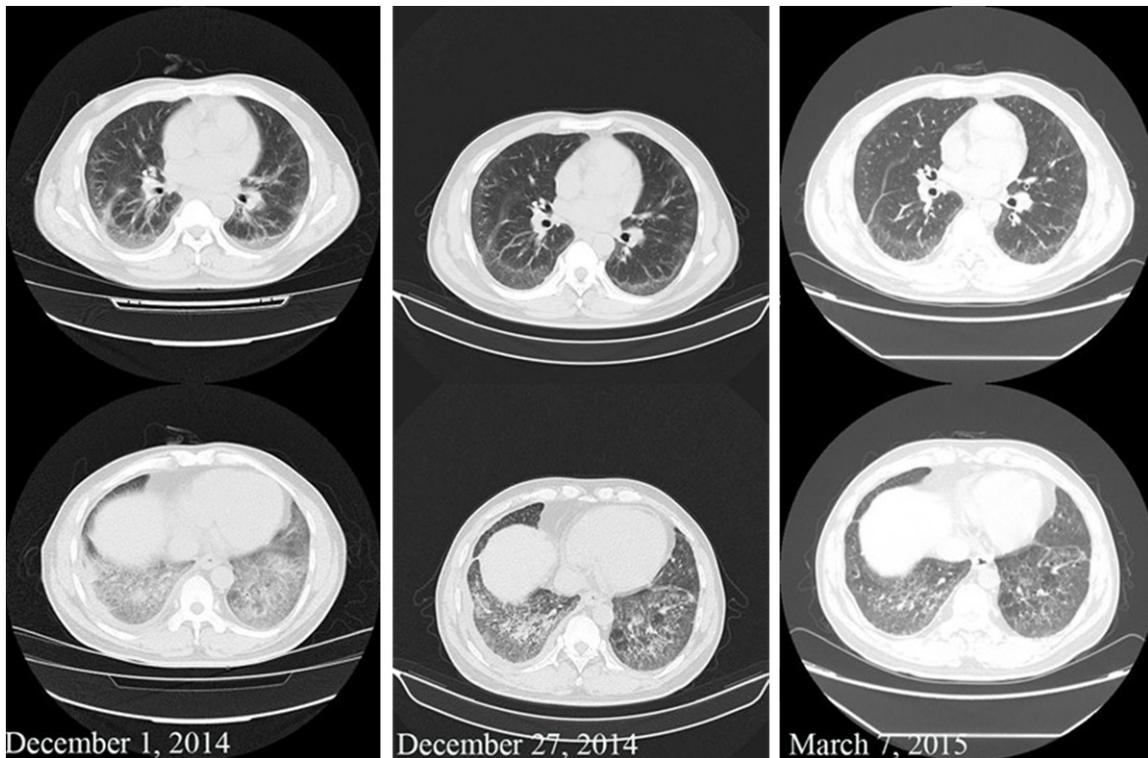
NSIP/OP, we report two cases of LD-CTD of NSIP/OP and review of some literature in the paper.

## Case 1

A 38-year-old gentleman male with a 2-year history of chapped skin of hands, 1-month right-sided pleuritic chest discomfort and weakness was presented to the Respiratory and Critical Care Medicine Department. His Chest X-ray and computed tomography scan revealed showed pulmonary fibrosis and right-sided pleural effusion. The complaint of chest discomfort relieved with administration of antibiotics over 15 days. Afterwards, he was transferred to our hospital for diagnosis. There was no long-term medication history and no exposure to occupational or agricultural lung diseases.

Physical examination revealed that chapped skin and "mechanics hands"-thick, cracked skin are usually seen on the palms and radial surfaces of the digits, and auscultation of the chest was identified an audible fine crackles.

The results of test T-SPOT. TB test was showed slightly elevated and the autoimmune serology



**Figure 1.** CT scan of the chest of Case 1. On admission, bibasilar distribution of ground-glass opacifications, consolidations predominantly in the lower lobes, and right pleural effusion on December 1, 2014. Pleural effusion and bilateral infiltrate gradually improved on December 27, 2014 and March 7, 2015.

test was positive to ANA and antibodies to Ro/SS-A (+++) and Ro-52 (++) . The results of deltoid muscle biopsy and hand biopsy were both negative.

His high resolution CT scan of the chest showed that ground-glass opacifications was bibasilar distribution of ground-glass opacifications, consolidations predominantly in the lower lobes, and right Pleural effusion (**Figure 1**: December 1, 2014). On Dec. 12th, 2014, the patient underwent thoracoscopy that revealed pleural cavity fiber exudative inflammation and characteristics of NSIP overlapped OP (**Figure 3A1** and **3A2**), however there were no evidence of tuberculosis granuloma.

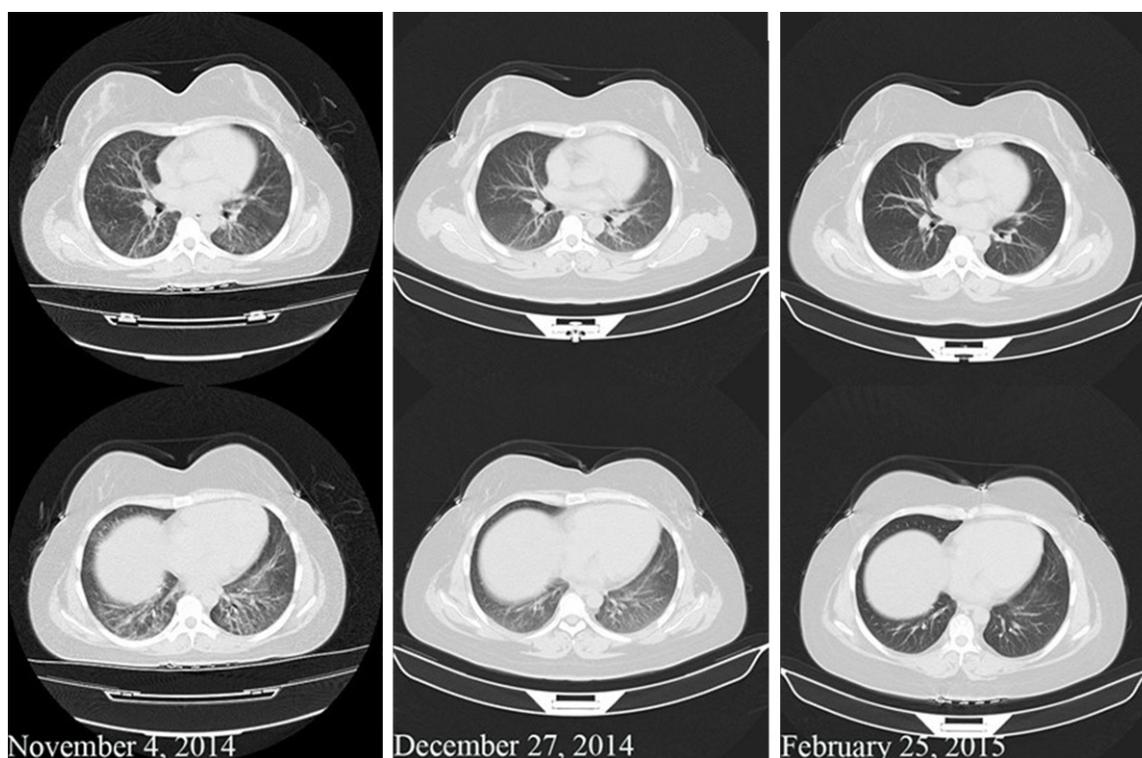
Then, we diagnosed this patient as a lung-dominant connective tissue disease- NSIP/OP. 40 mg of methylprednisolone intravenous was administered over 7 days, and gradually reduced to oral 24 mg methylprednisolone for 1 month, his chest high resolution CT scan showed Pleural effusion and bilateral infiltrate were improved. The patient has been followed for 3 months and his serial regular chest imaging show **Figure 1**.

#### Case 2

The second patient was a 24-year-old woman female who complained of dry cough and dyspnea and was diagnosed as having interstitial pneumonia at another hospital. She received oral traditional Chinese medicine over 3 months and her symptoms had little improvement in her symptoms. Afterwards, she experienced rapidly progressive extension of dry cough and dyspnea, and she was transferred to our hospital.

The physical examination revealed the patient with oral lips cyanosis, Reynaud disease, and crackles in the lower pulmonary lobes. Arterial blood gas analysis demonstrated the patient was respiratory failure with severe hypoxemia (pH 7.43; PaCO<sub>2</sub> 35 mmHg; PaO<sub>2</sub> 50 mmHg; FiO<sub>2</sub> 21%). The autoimmune serology test was nucleolus-ANA (ANA (1:800). And BALF show 10% neutrophils, 4% eosinophils, 56% lymphocytes, monocytes by 30% respectively.

The pulmonary function test revealed that the normal vital capacity was of 2.02 L (34.5% of predicted), with decreased diffusing capacity of



**Figure 2.** CT scan of the chest of the second case. On admission, diffuse ground glass, many patchy and consolidations along Bronchial blood vessel bundle with bilateral lower lobes predominance on November 4, 2014. Bilateral ground-glass consolidations evidently reduced on December 27, 2014 and February 25, 2015.

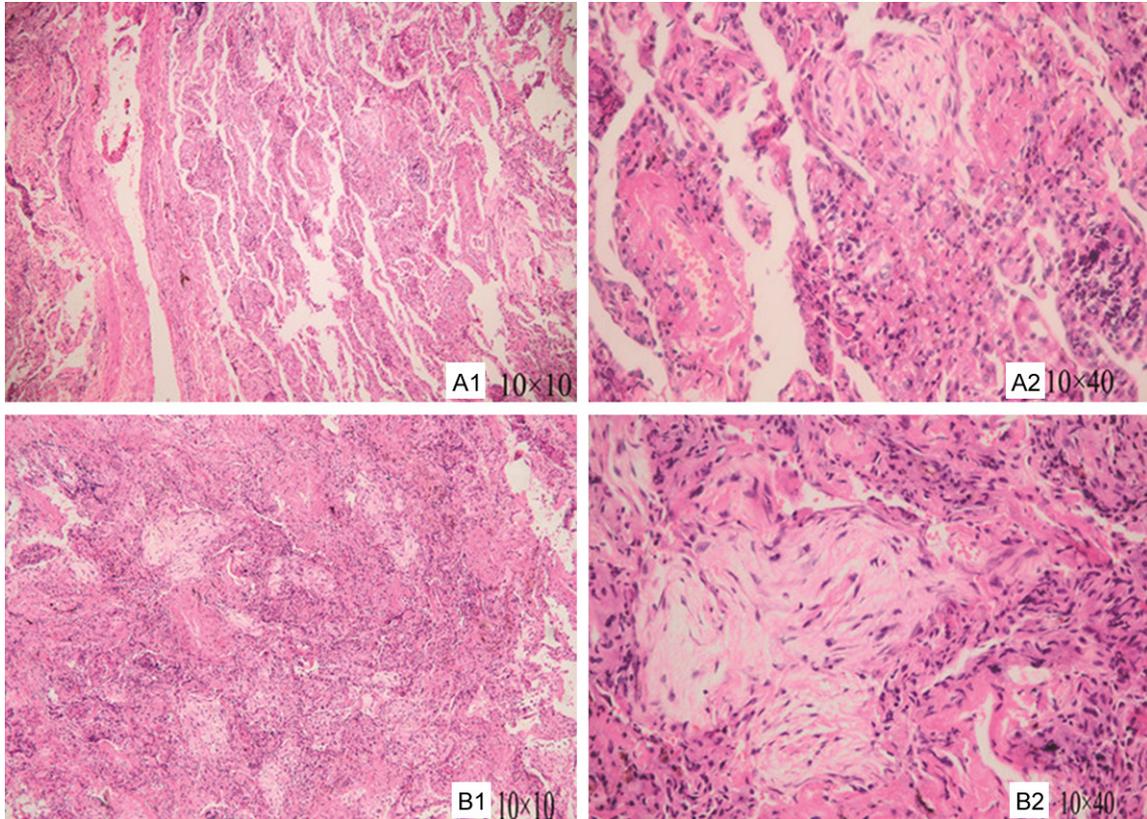
5% of predicted. Chest computed tomography images revealed diffuse ground glass, many patchy and a consolidation along Bronchial blood vessel bundle was predominantly in bilateral lower lobes predominance (**Figure 2**: November 4, 2014). Subsequently, a lung biopsy was taken by thoracoscopic surgery, which showed obvious abnormality in the lung (**Figure 3B1** and **3B2**). Multiple tissues were taken for biopsy using the thoracoscope, which shown showed cellular form NSIP overlapped OP. Finally, the patient was diagnosed as Lung-dominant connective tissue disease- NSIP/OP according to the above characteristics.

The treatment with low-dose methylprednisolone for 3 months improved her symptoms and her chest radiograph showed the bilateral ground-glass consolidations were evidently reduced (**Figure 2**). Repeat detailed lung function and arterial blood gases had improved dramatically (**Table 1**).

#### Discussion

A number of patients could clinically present with some manifest of CTDs, yet they do not

meet criteria for a defined CTD according to accepted criteria, in whom, it seems that the lung is the only or most clinically important manifestation of an undifferentiated CTD in these patients, which are suspected of having a systemic autoimmune disease, identified by the presence of circulating autoantibodies, specific histopathological features on surgical lung biopsy samples, or subtle extrathoracic manifestations. In 2010, Fischer A et al. [3, 4] proposed the criteria of lung-dominant CTD and, these patients could be classified as having lung-dominant CTD. It had not been widely accepted, but that was promoted clinical and scientific research on interstitial lung disease (ILD). Furthermore, the criteria is objective and measurable, and nonspecific symptoms (e.g., myalgias, arthralgias, esophageal reflux disease), nonspecific inflammatory markers (e.g., erythrocyte sedimentation rate), and low-titer ANA or RF are not included. Without the criteria, the above two cases only could be diagnosed as Unclassifiable IIP according to the International Multidisciplinary Classification of the Idiopathic Interstitial Pneumonias in 2013 ATS/ERS [5], And they were only administered



**Figure 3.** Histopathologic pictures of lung biopsies of two cases. A1 and A2: Markedly thickened with collagen fiber and blood vessel hyperplasia and diffuse alveolar wall thickening by uniform fibrosis with had interstitial lymphocyte inflammatory cells infiltration and some alveolar space organized in case 1. B1 and B2: Inflammation of the cells of the interstitium and granulation tissue, the Masson bodies that fill bronchiolar Lumina and extend into the alveolar ducts and spaces in second case.

**Table 1.** Detailed lung function tests and arterial blood gases

	Prior treatment	2 weeks later	1 month later	2 months later
<b>Lung function tests</b>				
FEV1%	32.8	39.1	52.7	59.8
FVC%	30.9	37	50.5	60.1
FEV1/FVC	92.6	92.05	90.95	85.83
VC%	30.7	36.9	50.3	60.4
DLCO%	not detected	15.3	25.7	30.3
<b>Arterial blood gases (FiO<sub>2</sub> 21%)</b>				
PaCO <sub>2</sub> (mmHg)	35	33	36	36
PaO <sub>2</sub> (mmHg)	50	72	77	80

DLCO = diffusing capacity for carbon monoxide, FEV1 = forced expiratory volume in 1 sec, FVC = forced vital capacity, RV = residual volume, TLC = total lung capacity, VA = alveolar volume, VC = vital capacity.

glucocorticoid treatment, which had poor prognosis and were easy to relapse. However, we had enough evidence to prescribe them glucocorticoid and immunosuppressant if they were

LD-CTD, which could have good therapeutic effect. Our two cases were a perfect example illustration.

The concept of NSIP has gradually evolved gradually over the past 20 years. Before the era of histopathologic classification of idiopathic interstitial pneumonias (IIPs), by Katzenstein 1994, IPF and NSIP were considered to be the same disease. NSIP was first described as an unclassified group of idiopathic interstitial pneumonias in

1994 [6]. Subsequently, many literatures have shown that NSIP had its differentiation from usual interstitial pneumonia (UIP) carries major prognostic implications. In the 2002 ATS/ERS

consensus committee classification of the IIPs [7], NSIP was recognized as a specific clinicopathological pattern, and in the 2013 update [5], idiopathic NSIP was accepted as a distinct clinical entity, while the NSIP pattern was recognized to be observed in a variety of settings, including CTD, HP, and drug toxicity, and in some patients with familial pulmonary fibrosis. The definition of organizing pneumonia has also experienced a long and complex history. In 1985, Epler et al. [8] analysis 2500 lung biopsies and discovered 57 organizing pneumonia patients with histopathologic manifestation that granulation tissue, the Masson bodies, that fill bronchiolar lumina and extend into the alveolar ducts and spaces, and then they provided a classic description of the disease under the term 'bronchiolitis obliterans organizing pneumonia'. The ATS/ERS consensus [7] committee recommended that idiopathic organizing pneumonia was defined as COP and other diseases associated organizing pneumonia was bronchiolitis obliterans organizing pneumonia.

Pathological studies about Lung fibrosis detected some biopsies shown NSIP overlap OP along bronchial blood vessel bundle with bilateral the lower lobes subpleural region predominance. In 2004, Tansey et al. [9] reviewed 54 lung biopsies from 37 Connective tissue disease-associated interstitial lung disease patients, shown 3 of 13 polymyositis/dermatomyositis and 1 of 17 rheumatoid arthritis were NSIP/OP. Afterwards, Marianne-Kambouchner et al. [10] analyzed 136 patients with biopsy-proven NSIP and 8 patients were NSIP/OP. Some other researches [11] reported that NSIP/OP histological pattern were mostly discovered in Sjogren syndrome, PM/DM and other rheumatic diseases, but were not reported in LD-CTD, and our two cases of NSIP/OP conform to LC-ILD according to Proposed Provisional Criteria for Lung-Dominant CTD in 2010.

In addition, we should pay attention on to the radiological features of NSIP/OP, which is the bibasilar distribution of ground-glass opacifications suggestive of nonspecific interstitial pneumonia and the consolidative features suggesting organizing pneumonia, which seem hug or "pancake" the diaphragm, our. The two cases we reported two cases were in accord with its features. If we have some acquaintance with HRCT manifestation of NSIP/OP, it would

be helpful for diagnosis and treatment to patient who refused open-lung biopsy.

### Conclusion

Histological pattern of NSIP/OP was mainly discovered in Sjogren syndrome, PM/DM and other rheumatic diseases. Along with the criteria lung-dominant CTD proposed, it could bring opportunity and challenge for the diagnosis of ILD, it and could change the previous classification method of ILDs. In the paper, we reported two cases of NSIP/OP pathological type in LD-CTD, and it should expand disease spectrum of NSIP/OP pathological types in ILD. However large-scale study should be processed in the next step.

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### Disclosure of conflict of interest

None.

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