

## CASE REPORT

# A case of interstitial pneumonia associated with anti-PL-7 antibody in a patient with rheumatoid arthritis

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**Abstract :** A 65-year-old female had been treated rheumatoid arthritis (RA), interstitial pneumonia (IP) and nephrotic syndrome with prednisolone and cyclosporine. She was emergently admitted to our hospital due to the worsening exertional dyspnea and severe hypoxemia. Chest computed tomography (CT) showed new diffuse ground-glass opacities (GGOs) with slight consolidations along with bronchovascular bundle were observed in addition to pre-existing reticular shadows in both lungs with lower lobe-predominance. An acute exacerbation (AE) of pre-existing IP triggered by an infection was suspected, and the treatment with antibiotics and corticosteroid pulse therapy improved her general condition and chest radiological findings. Because some autoantibodies associated with acute/subacute onset IP have recently become available in clinic, we examined those including anti-aminoacyl tRNA synthetase (ARS) antibodies, and found that she was positive for anti-PL-7 antibody. We diagnosed her anti-synthetase syndrome (ASS) without symptom of myositis, and her IP was considered to be ASS-related. The careful consideration is necessary to precisely diagnose and treat the patients with RA-associated interstitial lung diseases as the several etiologies may be overlapped in the same patient. *J. Med. Invest.* 65 : 147-150, February, 2018

**Keywords :** *interstitial pneumonia, anti-aminoacyl tRNA synthetase antibody syndrome, anti-PL-7 antibody, rheumatoid arthritis*

## INTRODUCTION

Anti-aminoacyl-tRNA synthetase (ARS) antibodies are one of the myositis-specific autoantibodies. They include anti-Jo-1, PL-7, PL-12, OJ, EJ, KS, Zo and Ha antibodies that are mainly identified in the sera of the patients with polymyositis (PM)/dermatomyositis (DM) (1, 2). Anti-ARS antibody-positive cases complicate interstitial lung disease (ILD) at a high rate together with or without muscle symptoms and joint symptoms, which is called as anti-synthetase syndrome (ASS). In some cases with ASS, ILD is the only manifestation of the disease. It is reported that the connective tissue diseases, including ASS, often develop in combination with other connective tissue diseases in one patient (*i.e.* PM/DM with systemic sclerosis), although the detection and diagnosis of those diseases are difficult in many cases. Here, we report a rare case that the ASS diagnosed in a patient with rheumatoid arthritis (RA).

## CASE REPORT

A 65-year-old female had been diagnosed as RA in the previous hospital at the age of 57, and had started to receive bucillamine (BUC) and methotrexate (MTX). Afterwards, she had developed interstitial pneumonia (IP) of which the etiology was suspected to be MTX-related, therefore the MTX treatment was discontinued and IP was partly improved. Further, she developed nephrotic syndrome at the age of 59, and the result of renal biopsy suggested the

possibility of membrane nephropathy due to BUC. She also discontinued to take BUC, and alternatively started to take 10 mg of prednisolone (PSL) and cyclosporin A (CyA). After two years, gradual deterioration of IP was observed, and she was referred to our hospital. We reconfirmed the diagnosis of RA based on 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) rheumatoid arthritis classification criteria (3), as she had 11 or more joint involvement, highly positive of anti-cyclic citrullinated peptide (anti-CCP) antibody and rheumatoid factor (RF), and elevated C-reactive protein (CRP). Moreover, the joint ultrasonography showed the synovial thickening and fluid accumulation in her both hands. The deteriorating IP was considered to be RA-associated. Thus, the dose of PSL was increased to 30 mg, which was gradually decreased afterwards, and the dose of CyA was re-adjusted. With this treatment, she was free from disease progression for about four years.

However, she started to feel worsening exertional dyspnea triggered by the acute bronchitis, and was emergently admitted owed to severe hypoxemia two weeks later. On her admission, physical examination showed a body temperature of 37.3°C, heart rate of 100 beats per minute, a blood pressure of 101/74 mmHg, SpO<sub>2</sub> 92% on 8 L/min oxygen with a mask. Chest auscultation revealed fine crackles on both sides with no murmurs of heart sound. Chest X-ray showed ground-glass opacities (GGOs) and consolidations in both lung fields (Figure 1). In the chest computed tomography (CT), diffuse pan-lobular GGOs with slight consolidations along with bronchovascular bundle were newly observed in addition to reticular shadows which had been recognized only in subpleural areas from a year ago (Figure 2A, B). Laboratory findings were as follows : white blood cell counts, C-reactive protein (CRP), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6), serum surfactant protein (SP)-A, and SP-D were elevated. Anti-nuclear antibody, anti-centromere antibody, anti-CCP antibody, RF, and anti-ARS antibody were positive (Table 1). Soon

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Figure 1. Chest X-ray of supine position on admission  
Chest X-ray on admission showed consolidations in the bilateral lung.

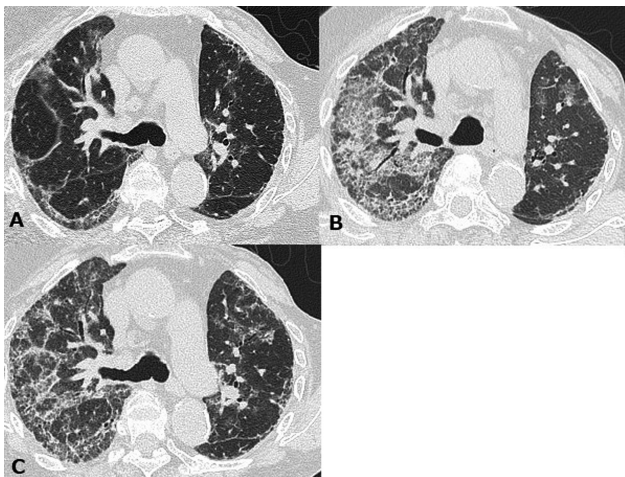


Figure 2. Chest computed tomography  
(A) Chest CT a year ago, when the activity of interstitial pneumonia was stable, which showed a reticular shadow under the pleura.  
(B) Chest CT on admission, which showed new bilateral ground-glass opacities.  
(C) Chest CT on 12 days after the treatments started, which showed that the bilateral ground-glass opacities were improved.

after, she required the high flow nasal cannula oxygen therapy with oxygen flow to 50L/min and FiO<sub>2</sub> to 0.4. Under the diagnosis of the acute exacerbation (AE) of pre-existing IP caused by an infection, the administration of intravenous tazobactam/piperacillin (13.5 g per day), Levofloxacin (500 mg per day) and corticosteroid pulse treatment (methylprednisolone 1 g per day for 3 days) followed by 0.5 mg/kg/day of PSL were started. This treatment improved her general condition and chest CT findings (Figure 2C). She discharged after the home oxygen therapy was introduced.

Because some auto-antibodies associated with acute/subacute onset IP have recently become available in clinic, we examined those including anti-ARS and anti-melanoma differentiation-associated gene 5 (MDA5) antibodies after confirming that clinical examination with serum and sputum did not suspect the viral or

Table 1 Laboratory data on admission

Hematology		Serology	
WBC	17300 / $\mu$ l	CRP	9.53 mg/dl
neu.	92.4 %	ANA	$\times$ 640
lym.	4.3 %	$\beta$ -D-glucan	< 6.0 pg/ml
mono.	2.7 %	PR3-ANCA	(-) U/ml
eos.	0.2 %	MPO-ANCA	(-) U/ml
baso.	0.1 %	KL-6	1735 U/ml
RBC	3.96 $\times 10^4$ / $\mu$ l	SP-D	341 ng/ml
Hb	11.5 g/dl	SP-A	236.8 ng/ml
Ht	35.8 %	anti-dsDNA Ab	(-)
Plt	31.4 $\times 10^4$ / $\mu$ l	anti-SS-A Ab	(-)
		anti-Centromere Ab	(+)
		anti-CCP Ab	477 U/ml
Biochemistry		anti-RNP Ab	(-)
AST	13 IU/l	anti-Sm Ab	(-)
ALT	8 IU/l	anti-Jo-1 Ab	(-)
ALP	227 IU/l	anti-Scl-70 Ab	(-)
LDH	13 IU/l	anti-MDA5 Ab	(-)
CK	41 IU/l	anti-ARS Ab	(+)
T-bil	0.5 mg/dl	anti-PL-7 Ab	(+)
BUN	18 mg/dl	RF	1354 IU/ml
Cre	0.58 mg/dl		
Na	144 mEq/dl	Arterial Blood gas analysis (HFNCOT FiO <sub>2</sub> 0.5)	
K	5 mEq/dl	pH	7.44
CL	106 mEq/dl	PaCO <sub>2</sub>	42.8 Torr
		PaO <sub>2</sub>	79.6 Torr
		HCO <sub>3</sub> <sup>-</sup>	28.7 mmol/l

Abbreviations : Ab, antibody ; ALP, alkaline phosphatase ; ALT, alanine aminotransferase ; ANA, anti-nuclear antibody ; ANCA, anti-neutrophil cytoplasmic antibody ; ARS, anti-aminoacyl-tRNA synthetase ; AST, L-aspartate aminotransferase ; BUN, blood urea nitrogen ; CK, creatine kinase ; Cl, chlorine ; Cre, creatinine ; CRP, C-reactive protein ; eos, eosinocyte ; Hb, hemoglobin ; HFNCOT, High flow nasal cannula oxygen therapy ; Ht, hematocrit ; K, potassium ; KL-6, Krebs von den Lungen-6 ; LDH, lactate dehydrogenase ; lym, lymphocyte ; mon, monocyte ; MPO, myeloperoxidase ; Na, sodium ; neu, neutrophil ; Plt, platelet ; PR3, proteinase 3 ; RF, rheumatoid factor ; SP, surfactant protein ; T-Bil, total bilirubin ; TP, total protein ; WBC, white blood cell ;  $\gamma$ -GTP,  $\gamma$ -glutamyl transferase.

bacterial infections (i.e., *Cytomegalovirus*, *Pneumocystis jirovecii*, etc.). The results showed that she was positive for anti-ARS and PL-7 antibodies without any other auto-antibodies except for RF and anti-CCP antibody (Table 1), indicating that IP in the present case was caused by ASS although it is difficult to completely distinguish it from RA-associated IP with nonspecific interstitial pneumonia (NSIP) pattern. The characteristics in chest CT findings showing GGOs and consolidations along with bronchovascular bundle is more compatible to IP associated with ASS (4). In addition, her clinical course with frequent relapse and good response to steroid therapy is consistent with IP with anti-ARS antibody (5). Based on these findings, we diagnosed her as ASS combined with RA.

## DISCUSSION

We experienced a case of acute exacerbation of IP which was considered to be associated with anti-PL-7 antibody-positive ASS

coexisting with RA.

RA patients with lung involvement are reported to mainly show usual interstitial pneumonia (UIP) or NSIP pattern (6), and the typical CT findings of chronic RA-related interstitial lung disease (RA-ILD) have been reported as follows: GGO, honeycombing shadow, linear/reticular opacities, centrilobular granular shadow, septal thickening/pleural thickening and traction bronchiectasies are frequently observed, but the consolidation and bronchovascular bundle thickening are relatively rare (7). However, regarding acute or subacute-onset RA-associated IP, organizing pneumonia (OP) and AE of pre-existing IP are common if infections and drug-induced lung injury are negligible (8). In the present case, chest CT findings showed diffuse pan-lobar GGOs which is consistent with AE of pre-existing IP, but not OP.

On the other hand, chest CT findings of patients with anti-ARS-ILD were reported that: 1) the distribution of opacities was seen predominantly in peripheral and/or peribronchovascular area (4), 2) the opacities with lower lobe-predominance often led the lungs to lose their volume (so called "shrinking lung") (9, 10), 3) unlikely to form honeycombing shadow and centrilobular granular shadow, 4) therefore the pattern of CT findings was considered to be non-specific interstitial pneumonia (NSIP) pattern with or without organizing pneumonia (OP) pattern.

In the chest CT findings of the present case, GGOs and slight consolidations along with the pleura and bronchovascular bundle were more evident, and linear reticular shadow and traction bronchiectasis were observed with the lower lobe-predominance, however, honeycombing shadow and centrilobular granular shadow were not obvious. Firstly, we considered the acute exacerbation of RA-IP, but there was reported that NSIP pattern of RA-IP have few case of acute exacerbation (7). Considering the typical differential patterns of IP among connective tissue diseases, CT findings in the present case seemed to be more consistent with anti-ARS-ILD rather than RA-ILD.

Moreover, the present case had twice AE of IP but relatively good response to corticosteroids. Yoshifuji *et al.* reported that anti-ARS antibody positive-ILD had a good response to corticosteroids, but more frequently recurrence (5). This clinical course applies to this case, and it is also one of the reasons why we diagnosed her as anti-ARS-ILD.

Regarding the positivity of anti-ARS antibody in RA patients, Nakashima *et al.* reported that anti-ARS antibodies were detected in 30.8% of idiopathic inflammatory myopathy patients whereas those were detected in only 4% of RA patients (11), suggesting that the positive rate of anti-ARS antibody in RA patients is relatively low (12-15). Currently, it is not known why anti-ARS antibodies become positive in RA patients. Ishikawa *et al.* reported the case that the treatment with TNF- $\alpha$  inhibitor was possibly the trigger to develop ASS in an RA patient (15). Because the positive rate of anti-ARS antibody in RA patients is low, more clinical experiences are needed to elucidate the etiology of anti-ARS antibodies in RA patients. On the other hand, Nakajima *et al.* reported that, among 12 patients with inflammatory myositis accompanied with RA, 8 patients had IP and all of them had anti-ARS antibody (16). This suggests that IP of RA patients may be associated with ASS rather than with RA.

Among anti-ARS antibodies, the most frequently detected antibody is anti-Jo-1 antibody (approximately 30%), followed by the others including anti-PL-7 antibody with the positive rate of 2-5% (17, 18). In patients with anti-PL-7 antibody, myositis and arthritis may be less frequent and milder than in those with anti-Jo-1 antibody (19, 20). In this context, as it was the case in our patient, it seems important to search for anti-PL-7 antibody in addition to other anti-ARS antibodies in patients with ILD to detect an underlying ASS, since this finding influences the treatment and prognosis of the patient (21-23).

In conclusion, we experienced a case of IP which was considered to be associated with anti-PL-7 antibody-positive ASS in patient with RA. The careful examination is necessary to precisely diagnose and treat the patients with RA-associated ILD as the several etiologies may be overlapped in the same patient.

## CONFLICT OF INTEREST

The authors have no conflict of interests directly relevant to the content of this article.

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