Acta Med. Okayama, 2016
Vol. 70, No. 3, pp. 217–221

Acta Medica Okayama
http://escholarship.lib.okayama-u.ac.jp/amo/

Case Report

Increased Serum KL-6 Levels Induced by Pulmonary Mycobacterium Avium Complex Infection in a Patient with RA-associated Lung Disease

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KL-6 is a glycoprotein found predominantly on type II pneumocytes and alveolar macrophages, and often shows increased serum levels in patients with interstitial pneumonia. We report a case of mycobacterium avium complex (MAC) infection whose disease activity was correlated with KL-6 levels in serum. During treatment of rheumatoid arthritis (RA)-associated interstitial lung disease (ILD) with prednisolone, chest image findings improved in association with decreased KL-6 levels. Following tapering of prednisolone, chest image findings deteriorated again as levels of KL-6 increased, suggesting recurrence of RA-ILD. Bronchoscopic examination revealed active MAC infection. Treatment of MAC infection not only improved chest image findings but also decreased KL-6 levels in serum, suggesting that KL-6 was increased by active MAC infection by itself, not by recurrence of RA-ILD. To the best of our knowledge, this is the first documentation of KL-6 elevation in serum in association with active MAC infection.

Key words: KL-6, mycobacterium avium complex, pulmonary nontuberculous mycobacterium infection, rheumatoid arthritis-associated interstitial lung disease, bronchial alveolar lavage

Pulmonary involvement is a common extra-articular feature of rheumatoid arthritis (RA). While chest manifestations are varied, interstitial lung disease (ILD) is the primary pulmonary characteristic of RA, often associated with increased levels of KL-6 in serum. Mycobacterium avium complex (MAC) is the most common cause of pulmonary disease worldwide among nontuberculous mycobacterium (NTM); however, little is known about the association of NTM infection with serum levels of KL-6.

Here, we report a case of pulmonary MAC infection associated with increased serum KL-6 levels while under treatment for RA-ILD. Increased KL-6 levels suggested worsening of ILD. However, the patient was diagnosed with pulmonary MAC infection. Treatment for MAC infection not only improved chest image findings, but also decreased KL-6 levels, suggesting that pulmonary MAC infection by itself increased KL-6 serum levels.

Received September 16, 2015; accepted January 4, 2016.
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Conflict of Interest Disclosures: No potential conflict of interest relevant to this article was reported.

Case Report

A 30-year-old female with RA, diagnosed based on ACR/EULAR criteria, was admitted to our hospital due to aggravation of image findings. The patient had no history of smoking. She had been diagnosed with RA-ILD, compatible with organized pneumonia (OP) pattern, based on chest image findings, clinical course, increased serum KL-6 levels, and increased number of lymphocytes in bronchial alveolar lavage (BAL) fluid one and a half years ago. Treatment of oral prednisolone 20 mg/day was initiated. The treatment went well, and the dose of prednisolone was gradually decreased. RA was stable throughout the treatment course.

Six months after initiation of prednisolone treatment at a dose of 4 mg/day, however, chest image findings deteriorated and serum KL-6 levels increased. Sputum smear examination and culture test for mycobacteriosis were all negative. Methotrexate, which had been administered for rheumatic control, was discontinued on suspicion of drug-induced lung injury. The dose of prednisolone was increased, and tacrolimus was added for treatment of exacerbation of RA-ILD, but chest image findings and KL-6 levels showed no improvement.

The patient's vital signs on arrival were as follows: body temperature, 36.7℃; blood pressure, 102/68 mmHg; pulse rate, 93/min; respiratory rate < 20/min; and oxygen saturation, 96% (room air). She reported feeling slightly tired, but had few complaints about respiratory or joint symptoms. On auscultation, no crackles or wheezes were heard in either lung. A chest X-ray showed bilateral shadows and chest computed tomography (CT) scan further demonstrated infiltrates and granular patterns in bilateral middle to lower lobes (Fig. 1). Neither restrictive nor obstructive impairment was seen on pulmonary function test. Blood examination revealed leukocytosis (white blood cell count: 10,870/μl) with a leftward shift, probably due to prednisolone therapy. Inflammation reaction (C-reactive protein; CRP) was not increased, and liver and kidney functions were normal. Serum levels of surfactant protein-D (SP-D) were normal, and levels of sialylated carbohydrate antigen KL-6 (KL-6: 1,153 U/ml) in serum were increased. Serum levels of MMP-3 were slightly increased. Serum beta-D glucan, galactomannan antigen, and cryptococcal antigen were all negative. Repeated sputum examination for several months demonstrated no evidence of infection,

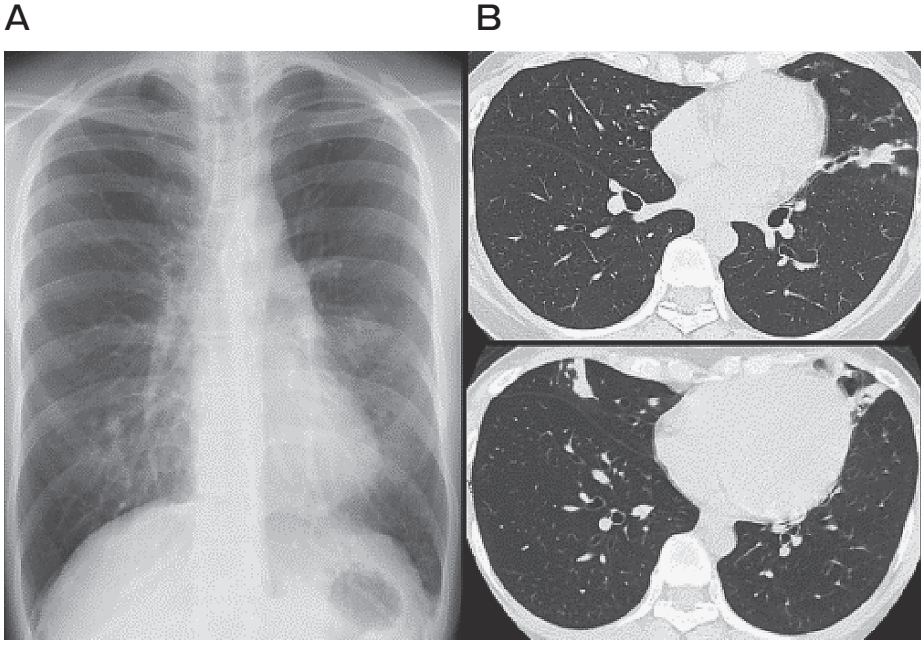

Fig. 1 Chest X-ray and CT images: A chest X-ray showed bilateral shadows in lower lung fields (A); infiltrates and granular patterns in bilateral middle to lower lobes were observed in chest high-resolution CT (B).

including NTM.

After admission, BAL was performed. The results revealed increased total cell number (3.5×10^5/ml) with a high ratio of lymphocyte (29%), and CD4/CD8 ratio in BAL fluid was increased (8.76). Direct smear examination of BAL fluid for mycobacterium infection demonstrated Gaffky 5 and culture examination proved nontuberculous mycobacterium infection (*M. avium*) (Table 1). Multi-drug therapy including clarithromycin (CAM; 600 mg/day), rifampicin (RFP; 450 mg/day) and ethambutol (EB; 500 mg/day) was initiated. Treatment was effective, and chest image findings improved, associated with decreasing levels of KL-6 in serum (Fig. 2).

Discussion

To the best of our knowledge, this is the first reported case of MAC infection in association with increased KL-6 levels in serum. Following treatment for MAC infection, chest image appearance improved, and KL-6 levels decreased. Therefore, active MAC infection by itself appeared to increase serum KL-6 levels, and disease activity of MAC was correlated with KL-6 levels in our case.

KL-6 is a glycoprotein found predominantly on type II pneumocytes and alveolar macrophages. Increased serum KL-6 levels in patients with interstitial pneumonia have been reported [1-3], and serum KL-6 elevation may be also caused by diseases such as hypersensitivity pneumonitis, pulmonary alveolar proteinosis, lung cancer, pneumocystis pneumonia and drug-induced pneumonia. Although there is a study describing increased KL-6 levels in epithelial lining fluid of patients with MAC infection [4], little is known about serum KL-6 levels in NTM, including MAC. A few studies have shown that serum KL-6 levels were significantly higher in the patients with pulmonary tuberculosis than in healthy controls [5]. The mechanism of how KL-6 secretion is increased in pulmonary tuberculosis remains uncertain. When type-2 pneumocytes and bronchial epithelial cells are stimulated or injured by mycobacterium tuberculosis infection, KL-6 might be more strongly expressed on the surface membrane. Further investigation, including clinical studies, will be necessary to clarify if KL-6 levels in serum of patients with pulmonary MAC infection are increased compared to healthy subjects, and if those levels are correlated with disease activity.

In the present case, underlying RA-ILD made MAC infection diagnosis difficult. The chest image findings affected with the RA-ILD OP pattern improved at first following treatment with prednisolone, with an associated decrease in KL-6 levels, suggesting that KL-6 levels were increased by RA-ILD alone. However, chest findings subsequently deteriorated with increased levels of KL-6. It has been reported that OP with elevated serum KL-6 is prone to disease recurrence and requires treatment with prednisolone

Table 1 Raboratory findings on admission.

Peripheral Blood						Pulmonary function test		
WBC	10,870	/μl	γ-GTP	16	IU/l	VC	2.52	L
Nt	92.3	%	LDH	195	IU/l	%VC	93.0	%
Ly	5.8	%	BUN	14.1	mg/dl	FEV1.0	2.23	L
Mo	1.7	%	Cr	0.68	mg/dl	FEV1.0%	84.8	%
Eo	0.1	%	Na	139	mEq/dl			
Ba	0.1	%	K	4.8	mEq/dl	BAL		
RBC	514	$\times 10^4$/μl	Cl	108	mEq/dl	Total cells	3.5	$\times 10^5$/μl
Hb	13.3	g/dl	CRP	0.07	mg/dl	Macrophages	65.0	%
PLT	33.4	$\times 10^4$/μl	RF	8.6	IU/ml	Ly	29.0	%
			MMP-3	86.1	ng/ml	Nt	6.0	%
Blood Chemistory			KL-6	1,153	U/ml	Eo	0	%
TP	6.8	g/dl	SP-D	73.7	ng/ml	Lymphocyte subset		
Alb	4.5	g/dl	β-D glucan	<6.0	pg/ml	CD4+/CD8+	8.76	
T.Bil	0.59	mg/dl	Aspergillus		(−)	Smea exam		(+)
AST	23	IU/l	Cryptococcus		(−)	Culture exam		M.avium
ALT	9	IU/l	QFT-3G		(−)			

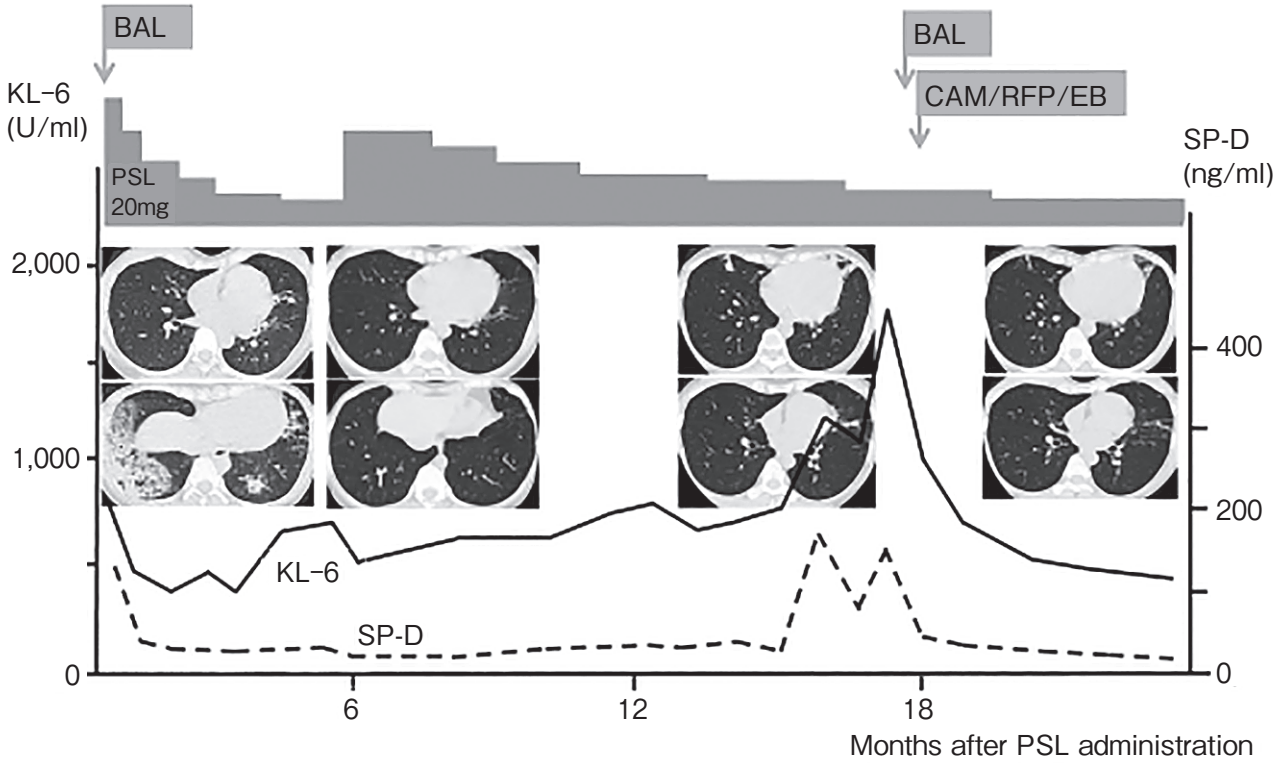

Fig. 2 Clinical course of treatment: The image findings deteriorated in association with serum KL-6 elevation, and showed no improvement with intensive treatment of RA-ILD such as prednisolone increase. Bronchoscopic examination including BAL revealed pulmonary NTM infection, and multi-drug therapy for pulmonary NTM was initiated. Granular shadows regressed and serum KL-6 levels decreased to normal level in several months.

[6]. Image findings and serum KL-6 elevation showed no improvement even with intensive treatment of RA-ILD, but were finally ameliorated by the treatment of NTM infection, with an associated decrease in KL-6 levels. Therefore, it appears that KL-6 levels were increased by MAC infection, not by recurrence of RA-ILD.

One might wonder whether underlying RA-ILD could affect the MAC-associated increase in KL-6 even though RA-ILD was well controlled by prednisolone therapy. RA-ILD with MAC infection might enhance secretion of KL-6 from alveolar type 2 cells even though RA-ILD was well controlled, and its secretion might be enhanced compared to MAC infection alone. To clarify this issue, it is necessary to compare KL-6 levels in NTM infection alone with NTM associated with stable RA-ILD.

ILD is the most common manifestation of rheumatoid lung disease [7-9], and is a source of substantial morbidity and mortality for affected patients. The chest manifestations of RA-ILD are varied and include pleuritis, pleural effusions, and airway diseases such as bronchiolitis obliterans, rheumatoid nodules and ILD [10]. In the present case, the chest image findings of MAC infection resembled RA-ILD, which made it difficult for us to diagnose MAC. Granular shadows had been also observed with consolidation at the time of the RA-ILD diagnosis, and both had improved by prednisolone therapy. Later, when granular shadows appeared and deteriorated, pulmonary MAC infection should have been a differential diagnosis; however, it can be difficult to distinguish RA-ILD from MAC infection simply with chest image findings. It is also unclear when this patient was infected with MAC. RA-ILD in this case had been well treated with prednisolone, with an associated decline of serum KL-6 levels, suggesting that pulmonary MAC infection was not very active when serum KL-6 stayed at low levels.

In summary, we experienced a case of pulmonary MAC infection in which serum KL-6 levels were cor-

related with disease activity of MAC in RA-ILD. The chest image findings of RA-ILD are complicated, and may resemble associated NTM infection, including MAC. This case indicates that pulmonary MAC infection should be included in the differential diagnosis when elevated serum KL-6 levels are observed, even in patients with RA-ILD.

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