

[ CASE REPORT ]

## The Onset of Eosinophilic Pneumonia Preceding Anti-synthetase Syndrome

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### Abstract:

A 66-year-old man had been treated with prednisolone for eosinophilic pneumonia for 8 years. His slowly progressing cough and dyspnea were accompanied by elevated levels of fibrotic serological markers and an increased reticular shadow on chest computed tomography images. The patient had recently tested positive for anti-EJ antibodies, a type of anti-aminoacyl-tRNA synthetase antibody; therefore, we diagnosed him with an exacerbation of interstitial pneumonia due to anti-synthetase syndrome (ASS). He was treated with tacrolimus and an increased prednisolone dosage. We herein present the first reported case of eosinophilic pneumonia preceding anti-EJ antibody-positive ASS.

**Key words:** anti synthetase syndrome, ARS, eosinophilic pneumonia, anti EJ antibodies, interstitial pneumonia

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### Introduction

Anti-synthetase syndrome (ASS) is characterized by the presence of anti-aminoacyl tRNA synthetase (ARS) antibodies accompanied by either interstitial pneumonia, dermatomyositis, polymyositis, arthritis, or Raynaud symptom (1). In ASS, interstitial pneumonia preceding other symptoms, such as those of the skin and joint, is difficult to diagnose and is often treated as an idiopathic interstitial pneumonia (IIP). Although eosinophilic pneumonia is known to precede rheumatoid arthritis and eosinophilic granulomatosis with polyangiitis (2, 3), its occurrence prior to ASS has not been reported. We herein present a case of worsening interstitial pneumonia with the development of anti-EJ antibodies during the treatment for eosinophilic pneumonia.

### Case Report

In 20XX, a 57-year-old man, with a medical history of bronchial asthma and smoking (33 pack-years) was admitted to our hospital for dyspnea. He was found to have eosinophilia and increased eosinophils in the broncho-alveolar lavage fluid (BALF). Hematologic tests revealed a white blood cell count of 10,100/mm<sup>3</sup>, comprising 22.2% eosinophils. The total cell count in the BALF was 2.6×10<sup>5</sup>/μL, comprising 5% macrophages, 5% neutrophils, 37% lymphocytes and 53% eosinophils; the ratio of CD4/CD8 was 0.39 in the BALF. Interestingly, an organizing pneumonia that manifested with eosinophilic infiltration was observed in the lung tissues obtained from video-assisted thoracoscopic surgery. Histologically, there was no evidence that suggested eosinophilic granulomatosis with polyangiitis. Staining for proteinase 3 anti-neutrophil cytoplasmic antibody and myeloperoxi-

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dase anti-neutrophil cytoplasmic antibody was negative. As a result, we initially reported this case as eosinophilic pneumonia with organizing pneumonia (4), and he was treated with oral corticosteroid therapy [prednisolone (PSL) 30 mg/day]. His daily PSL dose was reduced to 10 mg every other day in 20XX+4. The reticular shadow seen on his chest radiograph remained unchanged for more than five years (Fig. 1A). The eosinophil counts decreased to 100/mm<sup>3</sup> quickly and then increased again to 300-1,000/mm<sup>3</sup> over the next 8 years (Fig. 1B).

In 20XX+8, the patient complained that his cough and dyspnea were worse than in the previous year. He had been affected by noticeable mechanic's hands since 20XX+5 and was diagnosed with arthralgia in the shoulder and knee in 20XX+8. He had not been treated with any additional drugs since 20XX. Hematologic tests revealed a white blood cell count of 10,400/mm<sup>3</sup> with 1.7% eosinophils. The Krebs von den Lungen (KL)-6 and surfactant protein-D (SP-D) levels had gradually increased from those in 20XX+6 and were accompanied by a decreased pulmonary function (Fig. 1C and D). Chest computed tomography (CT) revealed a slowly progressive reticular shadow with traction bronchiectasis in the peripheral lung fields (Fig. 2), despite normal eosinophil counts (Fig. 1B), along with physical findings such as mechanic's hand and arthralgia. These findings suggested connective tissue disease (CTD), so the patient underwent an examination of serum autoantibodies. It has recently become possible to measure anti-ARS antibodies, and he was found to be seropositive for anti-ARS and anti-EJ antibodies with non-elevated levels of serum creatine kinase (CK) and aldolase (Table). Physical findings included fine crackles in the bilateral lung fields, mechanic's hands on the fingers of both hands, and arthralgia in the shoulder and knee. Since he did not have Gottron's sign or Raynaud's symptoms, he was diagnosed with ASS. A BALF examination was not performed at this time.

Immunosuppressive therapy with tacrolimus (4 mg/day) was initiated, in addition to increasing the PSL dosage (25 mg/day), for ASS. Subsequently, pulmonary function tests showed slight improvement in the vital capacity (VC), forced vital capacity (FVC), and diffusing capacity of the lung carbon monoxide (DLCO), and the images of interstitial pneumonia were also slightly improved (Fig. 2, right panel). Currently, he is being treated with PSL (10 mg/day) and tacrolimus (2 mg/day) without worsening of the interstitial pneumonia for more than 10 months after the diagnosis of ASS.

## Discussion

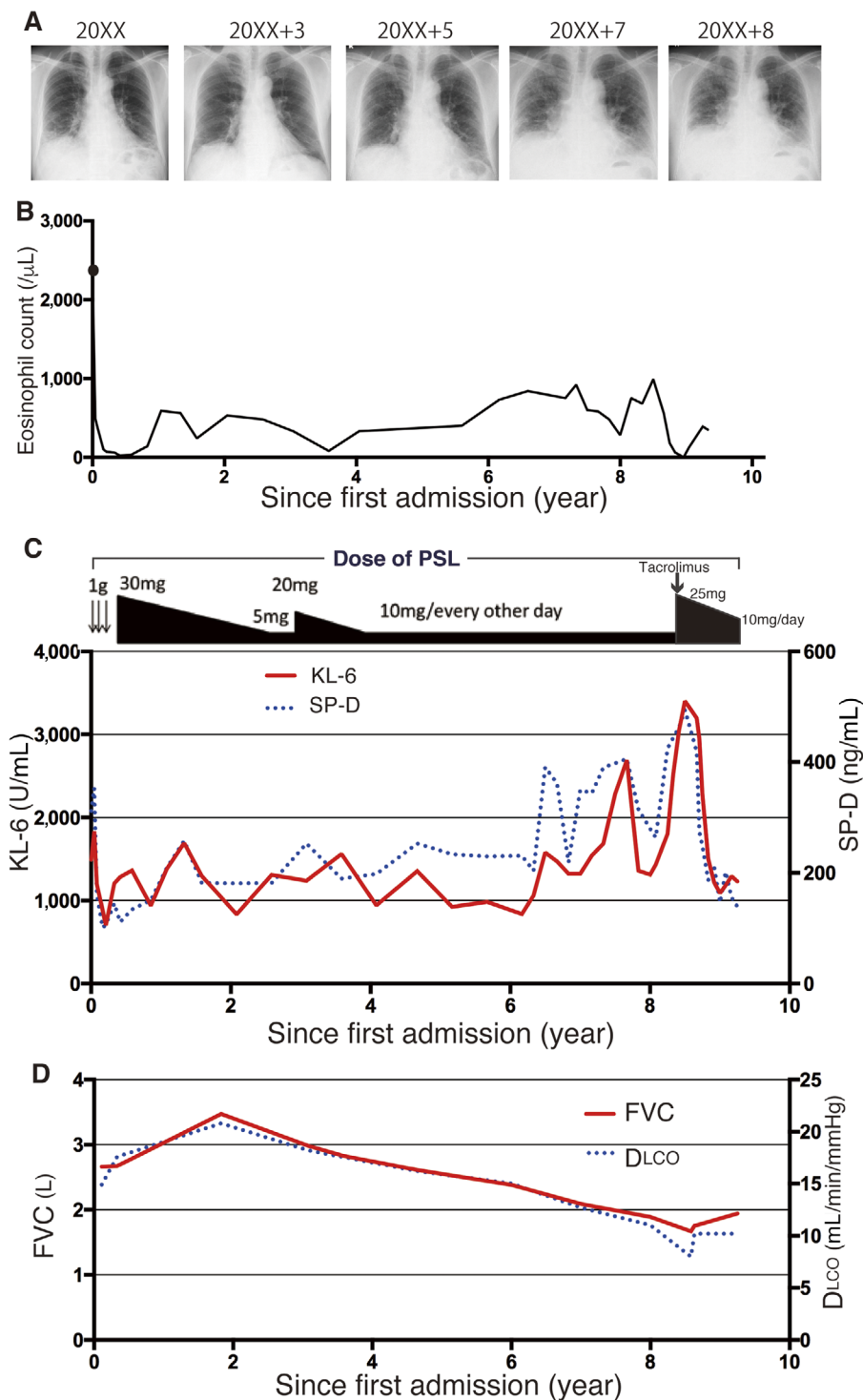
We present a case of ASS preceding eosinophilic pneumonia. We diagnosed eosinophilic pneumonia with organizing pneumonia through a surgical biopsy approximately nine years earlier (4). The patient had been treated with steroids as a single agent for more than eight years. Subsequently, the interstitial pneumonia worsened, accompanied by an ele-

vation of fibrotic markers, including KL-6 and SP-D. He was also found to be positive for anti-ARS antibodies and had typical mechanic's hands on the fingers of both hands; therefore, he was diagnosed with ASS and treated with an increased corticosteroid dosage and an immunosuppressive drug.

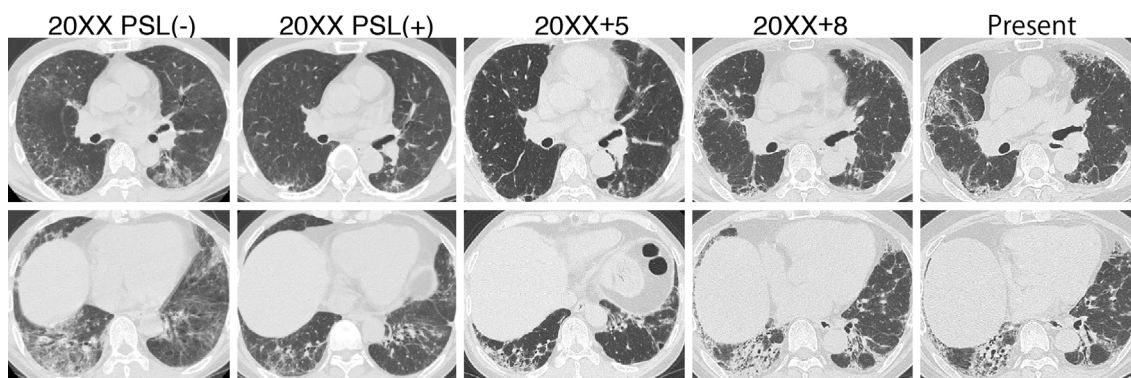
It has been reported that non-specific interstitial pneumonia (NSIP) is frequently found as a complication in patients positive for anti-ARS antibodies (5). Hamaguchi et al. examined the anti-ARS antibodies in Japanese patients and reported that the anti-EJ antibodies comprised 23% of the anti-ARS antibody-positive samples, most of which originated from patients who had preceding symptoms of muscle inflammation rather than classical or clinically amyopathic dermatomyositis (6). Patients who are positive for anti-EJ antibodies often have dermatological symptoms that manifest as a heliotrope rash and Gottron's sign. In addition, interstitial pneumonia also manifests in more than 80% of patients at the time of the diagnosis (7). In contrast, the occurrence of mechanic's hands, in the absence of skin symptoms, is observed in ASS patients who are similar to the present case (8). Therefore, attention should be directed to those who present with a combination of mechanic's hands and NSIP, which may suggest ASS with interstitial pneumonia.

CTD is sometimes accompanied by interstitial pneumonia in the absence of other symptoms that indicate CTD. The differential diagnosis of interstitial pneumonia is often difficult. Some entities characterized by interstitial pneumonia preceding CTD include undifferentiated connective tissue disease interstitial lung diseases (UCTD-ILD) (9), autoimmune-featured ILD (AIF-ILD) (10), and interstitial pneumonia with autoimmune features (IPAF) (11). Recently, Kono et al. reported that the clinical characteristics and survival rates of NSIP preceding the diagnosis of collagen vascular disease (CVD) and the initial diagnosis of NSIP with CVD were not markedly different (12). Chronic eosinophilic pneumonia is known to precede rheumatoid arthritis or eosinophilic granulomatosis with polyangiitis (2, 3); however, eosinophilic pneumonia preceding ASS has not been previously reported.

Although the possibility of ASS being complicated by eosinophilic pneumonia at its initial diagnosis has been proposed, methods for measuring anti-ARS antibodies were not widely available at the time of the diagnosis of the present case; he was therefore diagnosed with eosinophilic pneumonia. As such, whether or not ASS was complicated with eosinophilic pneumonia at the initial diagnosis of our case remains unclear. However, if a pulmonary lesion of ASS had already existed during the initial treatment, then interstitial pneumonia, treated with corticosteroid single therapy, would not have caused an exacerbation in 20XX+5 but not in 20XX when therapy was initiated. Therefore, it is plausible that ASS occurred during the treatment of eosinophilic pneumonia (around 20XX+5) in this case. However, the interstitial pneumonia has remained since 20XX despite the



**Figure 1.** The 9-year clinical course of eosinophilic pneumonia preceding ASS. **A:** Changes in the reticular shadow seen on chest radiography from 20XX to 20XX+8. **B:** A sustained decrease in serum eosinophil counts. **C:** The patient received a treatment of steroid pulse therapy prior to oral corticosteroid [Prednisolone (PSL): 30 mg/day] at first diagnosis. PSL was gradually reduced to 10 mg every other day in 20XX+4. Thereafter, serum fibrotic markers, including KL-6 and SP-D, began to increase in 20XX+6. Serum fibrotic markers decreased when PSL was increased and an immunosuppressive agent was added for treatment. **D:** Vital capacity, forced vital capacity, and diffusing capacity of the lung carbon monoxide slowly decreased from 20XX+2 to 20XX+8. One and 8 months after treatment with immunosuppression and increased prednisolone, the parameters of pulmonary function slightly improved.



**Figure 2.** Computed tomography images since the initial admission. Reticular shadows decreased after the administration of PSL in 20XX and clearly reappeared with traction bronchiectasis in 20XX+8. The reticular shadow did not disappear after the additional of an immunosuppression agent and increase of prednisolone (right panel).

**Table.** Laboratory Findings on Admission, and Pulmonary Function Tests.

<Hematology>		<Biochemistry>		<Serology>	
WBC	10,400 / $\mu$ L	TP	7.7 g/dL	Anti-Nuclear-Ab	<20
Neu	84.8 %	Alb	4.3 g/dL	Anti-Sm-Ab	(-)
Lym	10.8 %	T-bil	0.6 mg/dL	Anti-RNP-Ab	(-)
Mo	2 %	AST	28 U/L	Anti-SS-A-Ab	(-)
Eo	1.7 %	ALT	25 U/L	Anti-SS-B-Ab	(-)
Ba	0.7 %	LDH	289 U/L	Anti-Scl-70-Ab	(-)
RBC	476 $\times$ 10 <sup>4</sup> / $\mu$ L	ALP	230 U/L	Anti-CCP-Ab	18.4 U/mL
Hb	14.5 g/dL	$\gamma$ -GTP	42 U/L	Anti-MMP-3-Ab	168.5 ng/mL
Ht	42.9 %	CK	92 U/L	Anti-ARS-Ab	177.8 U/mL
Plt	30.4 $\times$ 10 <sup>4</sup> / $\mu$ L	BUN	9 mg/dL	Anti-Jo-1-Ab	(-)
		Cr	0.57 mg/dL	Anti-EJ-Ab	(+)
		Na	137 mEq/L	PR3-ANCA	(-)
		K	4.8 mEq/L	MPO-ANCA	(-)
		Cl	103 mEq/L		
		Ca	9.3 mg/dL	CRP	0.46 mg/dL
		BS	99 mg/dL	Ferritin	19.8 ng/mL
		HbA1c	5.4 %	Aldolase	8.7 U/L
				KL-6	3197 U/mL
				SP-A	87.3 ng/mL
				SP-D	419 ng/mL
<Coagulation>		<Blood Gas Analysis (room air)>			
PT%	94 %	pH	7.37		
PT-INR	1.02	PCO <sub>2</sub>	34.9 mmHg		
APTT	25.6 sec	PO <sub>2</sub>	96.3 mmHg		
Fibrinogen	310 mg/dL	HCO <sub>3</sub>	20.1 mmol/L		
FDP	3.8 $\mu$ g/mL	Base Excess	-5.1 mmol/L		
D-dimer	0.5 $\mu$ g/mL				
<Pulmonary function tests>					
VC	1.73 L				
%VC	49.9 %				
FVC	1.75 L				
FEV1.0	1.57 L				
FEV1.0%	89.71 %				
DLCO	10.21 mL/min/mmHg				

administration of corticosteroid therapy. We therefore believe that this case exhibited interstitial pneumonia as eosinophilic pneumonia, but not as chronic eosinophilic pneumonia, consistent with a previous report that described ASS combined with eosinophilic pneumonia.

Iijima et al. reported a case of ASS complicated by eosinophilic pneumonia at the initial diagnosis. Serologically, there was an increased number of eosinophils, and histopathologically, eosinophilic infiltration of the pulmonary tissue was noted (13). Since the overall clinical course

was steroid-resistant and not compatible with chronic eosinophil pneumonia, the authors suggested that it was possible the patient may have presented with eosinophilic pneumonia as a pulmonary manifestation of ASS. It has been reported that ASS cannot always be controlled using single corticosteroid therapy, and the addition of an immunosuppressive drug should be considered for the treatment of ASS (14). In our case, CT scans showed the recent worsening of interstitial pneumonia with traction bronchiectasis, which is slightly different from the findings of eosinophilic

pneumonia at the initial diagnosis. In addition, the recent clinical course was not accompanied by an elevation of peripheral eosinophilia, despite the reduced dose of corticosteroids. Furthermore, the patient had a stable clinical course while on single corticosteroid therapy for approximately more than five years. Therefore, this exacerbation of interstitial pneumonia may have been caused by the additional complications of ASS and was not a recurrence of eosinophilic pneumonia. However, there is a limitation to this case report describing eosinophilic pneumonia preceding ASS, and the accumulation of more cases will be needed in order to discuss the association between ASS and eosinophilic pneumonia.

In summary, we encountered a case of interstitial pneumonia accompanied by the presence of anti-EJ antibodies that was preceded by eosinophilic pneumonia. When eosinophilic pneumonia is resistant to treatment with a corticosteroid as a single agent, the association with CVD, as observed in ASS, should be considered.

**The authors state that they have no Conflict of Interest (COI).**

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