TITLE

ANTI-GLYCYL tRNA SYNTHETASE ANTIBODY ASSOCIATED INTERSTITIAL LUNG DISEASE WITHOUT SYMPTOMS OF POLYMYOSITIS/DERMATOMYOSITIS.

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RUNNING TITLE

Anti-EJ associated ILD

ABSTRACT

Anti-Glycyl tRNA synthetase (EJ) autoantibody is a form of eight anti-aminoacyl tRNA synthetase (ARS) antibodies which frequently associate with polymyositis (PM) and dermatomyositis (DM). Interstitial lung disease (ILD) rarely is an only disease among those patients in which patients with anti-EJ antibody are fairly common, however, their pathological features have never been described. Here, we report a case of anti-EJ antibody associated ILD without symptoms of PM/DM. A 56 year-old woman presented rapidly progressing dyspnea. Her radiograph showed ILD and wedge lung biopsy was taken for pathological diagnosis. The biopsy showed cellular and fibrotic ILD best fitting to non-specific interstitial pneumonia along with the features of acute lung injury. The patient was treated with high dose methylprednisolone followed by combination of prednisolone and cyclosporine, which showed good response.

KEYWORDS

anti-EJ antibodies, anti-aminoacyl-tRNA synthetase autoantibodies, acute lung injury, Pathology, pneumonia

INTRODUCTION

The anti-aminoacyl tRNA synthetase (ARS) antibody syndrome has large association with interstitial lung disease (ILD). The ARSs are a set of cellular enzymes, each of which catalyzes the formation of aminoacyl tRNA from a specific amino acid and its cognate tRNA. They can be found in; 25–35% of patients with the chronic inflammatory muscle disorders, polymyositis (PM) and dermatomyositis (DM)[1]. Autoantibody to glycyl tRNA synthase (anti-EJ) is a form of eight anti-ARS antibodies identified in patients with PM/DM. Each of these anti-ARS antibodies has been reported to be associated with a similar syndrome, anti-ARS antibody syndrome, characterized by myositis with a high frequency of interstitial lung disease (ILD) (50-80%), arthritis (50-90%), and skin lesions of the fingers referred to as "mechanic's hands" (70%)[2]. Among those symptoms, ILD is the most serious life-threatening complication. Some cases of ILD with anti-ARS-antibody were reported to have no symptoms of myositis[3]. The similarity of clinical features in patients with different anti-ARS antibodies is known, but some reports indicated that there are certain differences in clinical symptoms associated with each of the anti-ARS antibodies. Among eight anti-ARS antibodies, the most common antibody in all patients is anti-Jo-1 (35%), and anti-EJ positive patients are fewer (5-20%), but for the cases with ILD, anti-EJ is the most common antibody (20-35%)[2, 3]. Although pulmonary manifestations and radiological findings of ILD in patients with anti-EJ have been reported, no reports described pathological features. In this report we describe the radiological and pathological features of an anti-EJ antibody positive patient with ILD, who had the no symptoms of PM/DM.

CLINICAL SUMMARY

A 56-year-old woman presented progressive non-productive cough and dyspnea on exertion, with Medical Research Council dyspnea scale of grade 2, for 3 months. Her X-ray showed abnormal shadows. She was a never-smoker and had no significant medical history. She had no other environmental risk factors for respiratory disease except for the use of feather comforter. She was admitted to the hospital for the detail assessment of her respiratory problem.

On physical examination, fine crackles were heard on chest auscultation. Though Raynaud's phenomena, arthralgia, morning stiffness and xerostomia were found, they didn't fulfill the diagnostic criteria of any certain connective tissue disease. Table 1 shows laboratory data on admission. The blood gas analysis showed a mild hypoxia. The C-reactive protein level was elevated (2.90 mg/dl). The serum levels of Krabs von den Lungen-6 (KL-6) and surfactant protein-D (SP-D) were increased (1045 U/ml and 149.6 ng/ml, respectively). The patient's serum were positive for anti EJ antibody, but negative for antinuclear antibody, other types of anti-ARS antibodies, and other autoantibodies suggesting autoimmune disorders. Pulmonary function test showed slight respiratory disability and diffusion function disorder. Bronchoalveolar lavage (BAL) fluid with differential cell counts were performed in left B5. Total cell number was 5.69×10^5/ml, and lymphocytes dominated at 45% in which CD4/8 ratio was low as 0.19.

Sets of chest X-ray and high resolution computed tomography (HRCT) were obtained on admission and 2 months after the biopsy. Chest X-ray on admission revealed infiltrative shadows in the bilateral lung fields (Fig.1a) and chest HRCT showed diffuse ground-glass opacities and areas of air space consolidation along the bronchovascular bundles in the bilateral lung fields predominantly in the lower lobes (Fig.1c)

After the Video-assisted thoracic surgical (VATS) lung biopsy, due to rapid progression of the dyspnea, patient was treated methylprednisolone 1g/day for 3days followed by 40mg/day of Prednisolone with Cyclosporine A, 150mg/day, for 22 days. The amount of prednisolone and Cyclosporine A was gradually decreased thereafter. Due to the significant improvement of respiratory symptom and radiographic abnormality, the patient was discharged 70 days after her admission. No recurrent ILD was identified with 4 months' follow up.

Follow up chest X-ray and HRCT after one month of intense therapy with steroid and immunosuppressant showed remarkable improvement for both bilateral lung fields (Fig.1b, d).

PATHOLOGICAL FINGINGS

Video-assisted thoracic surgical (VATS) lung biopsy was performed to the left lower lobe superior segment, S6, and anterior basal segment, S8. Both specimens showed similar histological findings. Under the light microscope, the lesion was characterized by the pattern of nonspecific interstitial pneumonia (NSIP), showing diffuse expansion of the interstitium with moderate cellular inflammatory cell infiltration and mild increase of fibroblast in the alveolar septa. There was a slight centriacinar accentuation, but basically all areas of secondary lobule were diffusely affected. The area with complete normal lung parenchyma was not found. Addition to the findings typically seen in ordinary NSIP cases, acute inflammatory process such as exudative edema in both airspace and alveolar septa, presence of a few organizing pneumonia foci of Masson body type, scattered airspace fibrin, denudation of the pneumocytes, and enlargement of alveolar spaces due to collapse of most distal alveolar walls (Fig.2a-d). Hyaline membrane, hallmark of diffuse alveolar damage, was not found. Dense fibrosis suggesting background chronic fibrotic interstitial pneumonia such as usual interstitial pneumonia was not found, either. Although moderate degree of plasmacytosis was seen, other findings suggesting connective tissue disease, such as lymphoid follicle with germinal center, perivascular fibrosis, marked pleuritis, or chronic bronchiolitis, were not remarkable[4].

The skin biopsy was also performed from left forearm which did not show inflammatory changes suggestive of dermatomyositis.

Discussion

The VATS biopsy of our case showed cellular and fibrotic NSIP pattern along with remarkable amount of findings suggesting pathological acute lung injury (ALI). According to the previous reports, Yousem et al reported that usual interstitial pneumonia (UIP) was the most common pathological pattern in ILD with anti-Jo-1 antibodies followed by diffuse alveolar damage (DAD) and NSIP[5]. On the other hand, Fischer et al reported that majority cases of ILD with non-Jo-1 anti-ARS (PL-7 and PL-12) antibodies showed either NSIP with organizing pneumonia (OP) or OP with ALI[6]. The numbers of cases included in those reports are not enough to separate the two groups, however, our case may be reasonably similar to the latter series. Based on publications, the prognosis of ILD associated with anti-ARS antibodies seems favorable compared to those with anti-Jo-1 or anti-melanoma differentiation-associated gene (MDA) [5-7]. Histological absence of UIP pattern and/or DAD, poor prognostic signs, may be an important features of ILD with anti-ARS antibodies.

Another point of our case was about pathological ALI. The term ALI has been used for both clinically and pathologically in a slight different setting[8] in which ALI in pathology has been used for cases indicating acute to subacute lung inflammation more for the exudative conditions. When the term ALI is used in the pathological reports, it usually means that the pathological diagnosis of the case was not conclusive between OP and DAD[9]. The present case did not fulfill the criteria of DAD or OP by lacking hyaline membrane or diffuse Masson bodies. The diagnosis of NSIP did not fit well to the case considering the acute to subacute onset of the case, either. The current case may suggest that histological ALI, which do not fit any of DAD, OP, or NSIP, may be a characteristic feature. Cases with anti ARS antibodies may characteristically show more rapid and intense disease than ordinary NSIP, and that may be explained by the features of ALI.

Differences of pathology or prognosis between cases with and without PM/DM are not certain. More reports in this context will be needed. Although this case has not developed PM/DM with 10 months' follow up. The report published by Hamaguchi et al indicated that 29% of cases with ILD alone at initial presentation developed myositis with follow up[2]. In the present case, the patient was treated with intense corticosteroid and cyclophosphamide, which may have protected the patient from progression to PM/DM.

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DISCLOSURE

None of the authors have any financial and personal relationships with other people or organizations that could inappropriately influence.

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FIGURE LEGENDS

Figure 1

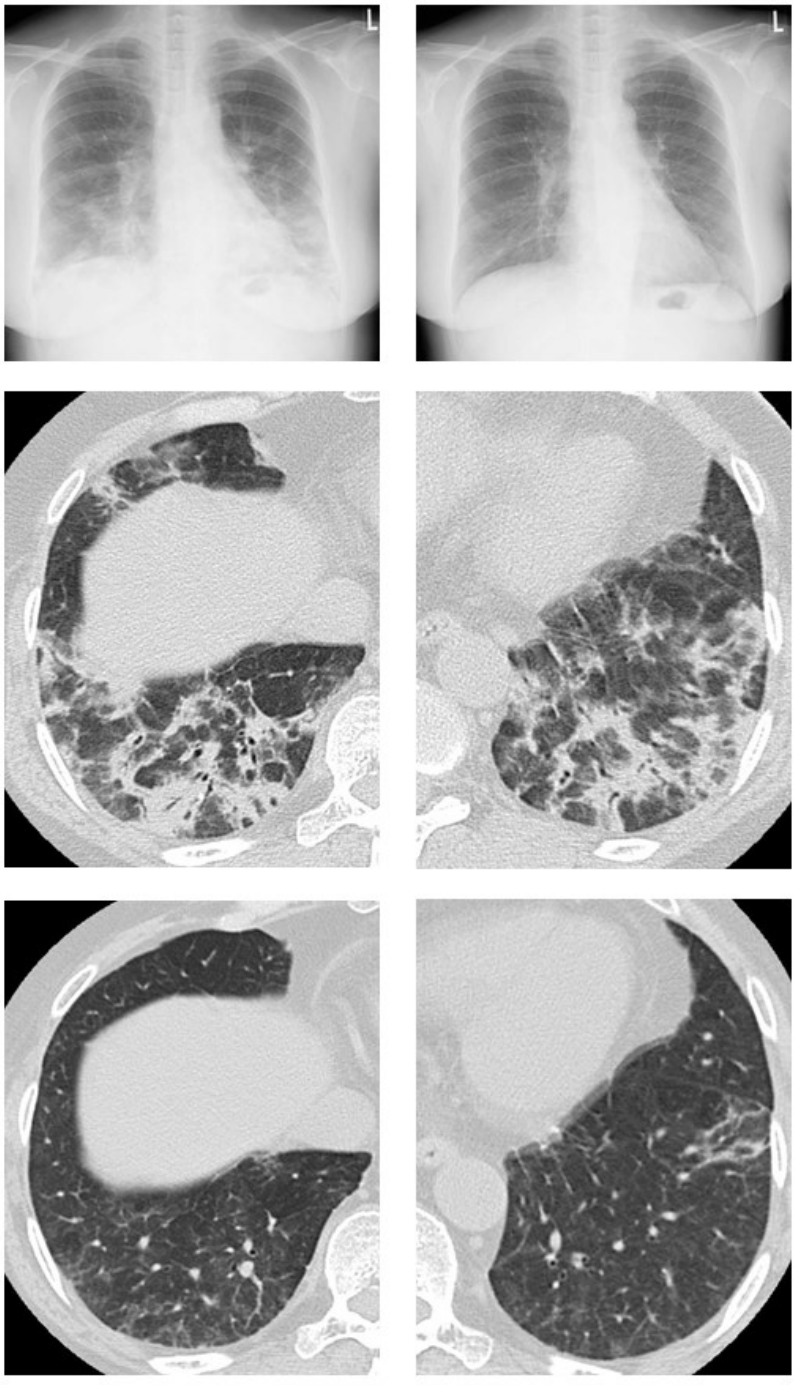

Figure 1

Chest X-ray on admission ,showing infiltrative shadows in the bilateral lung fields (a). Chest high resolution computed tomography on admission showed diffuse ground-glass opacities and areas of air space consolidation along the bronchovascular bundles in the bilateral lung fields predominantly in the lower lobes (c). Follow up chest X-ray and HRCT after one month of intense therapy with steroid and immunocompressant showed remarkable improvement for both bilateral lung fields (b,d).

Figure 2

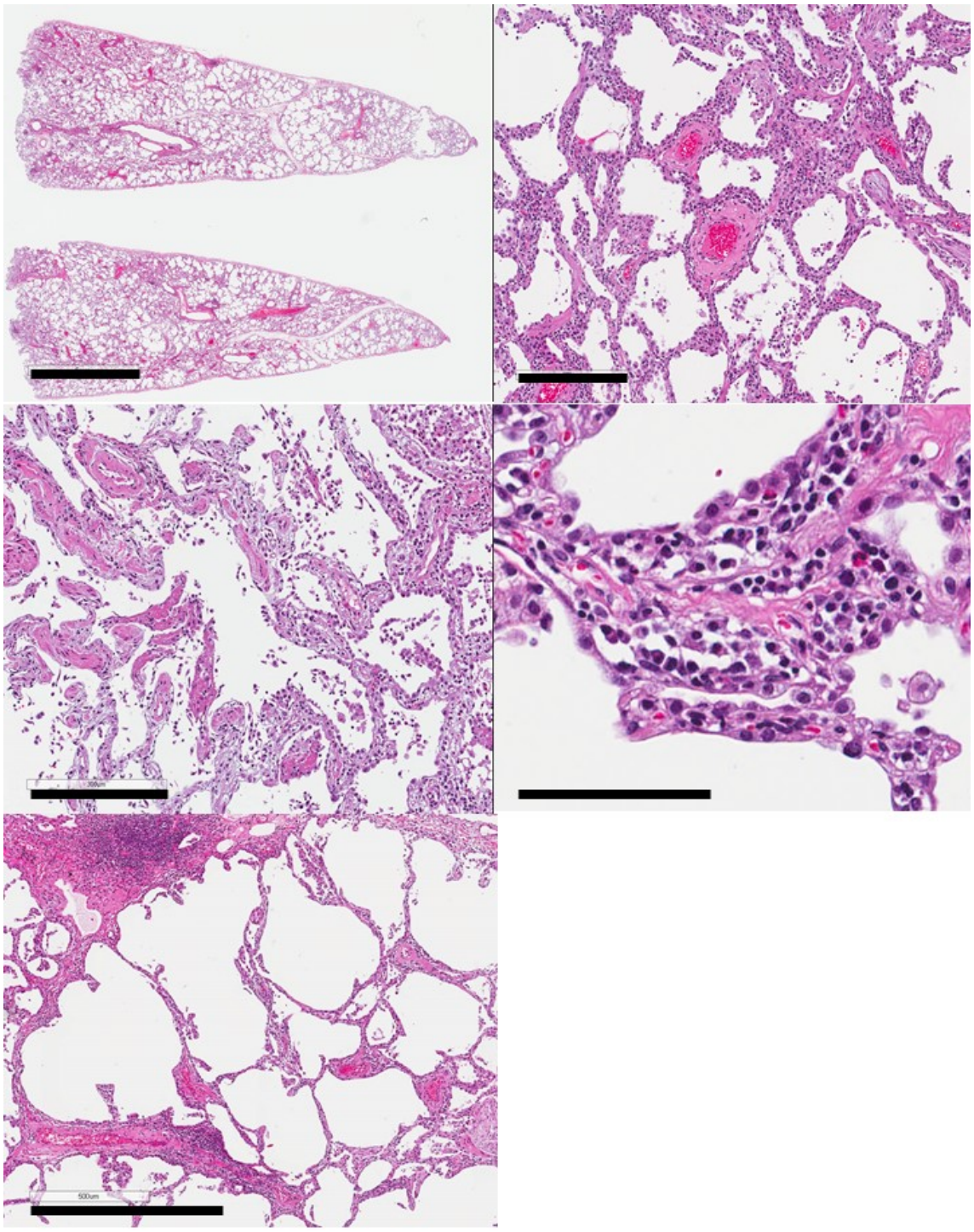

Figure 2

Histopathological findings of the case (a-e). (a) The low-power field of specimen showed diffuse abnormality. Enlargement of alveolar spaces due to collapse of distal alveolar septa is seen. Scale bar, 500um. (b) Expansion of the interstitium with mild to moderate cellular inflammatory cell infiltration and mild increase of fibroblast in the alveolar septa, characteristic findings of nonspecific interstitial pneumonia (NSIP), is seen in a diffuse manner. Exudative edema and organizing pneumonia are also found. Scale bar, 300um. (c) Area showing acute lung injury. Note airspace fibrin (arrows). Scale bar, 300um. (d) Denudation of the pneumocytes (arrow heads) and edema are seen in both airspace and interstitium. Scale bar, 200um.

TABLES:

Table 1. Laboratory data of the patient on admission.

<Arterial blood gas>		<Biochemistry>	
pH	7.424	TP	8.2 g/dl
PaO_2	74.5 Torr	AST	12 IU/U
$PaCO_2$	35.3 Torr	ALT	15 IU/U
		LDH	207 IU/L
<CBC>		γ-GTP	129 IU/L
White blood cells	8910 /mm^3	ALP	477 IU/L
Neutrophil	70%	CPK	41 IU/L
Lymphocyte	24.9%	BUN	10.6 mg/dl
Monocyte	3.4%	Cr	0.58 mg/dl
Eosinophil	0.9%		
Basophil	0.6%	<Pulmonary function test>	
		VC	2.01 l
<Serology >		%VC	79.1%
CRP	2.9 mg/dl	$FEV_{1.0}$	1.60
RF	negative	$FEV_{1.0}$/FVC	79.2%
Antinuclear antibody	<40	%DLco	78.6%
Anti-SSA antibody	negative		
Anti-SSB antibody	negative	<Bronchoalveolar lavage (left B^5)>	
Anti-scl-70 antibody	negative	Fluid recovery	100/150 ml
Anti-Jo1 antibody	negative	Recovered cell count	5.69×10^5/ml
Anti-EJ antibody	+	Macrophage	41%
Anti-ds-DNA antibody	negative	Lymphocyte	45%
KL-6	1045 U/ml	Eosinophil	5%
SP-D	149.6 ng/ml	Basophil	9%
		CD4/CD8 ratio	0.19

ALP = Alkaline Phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BUN = blood urea nitrogen; CKP = creatine phosphokinase; Cr = creatine kinase; CRP = C-reactive protein; DLco = diffusion capacity; FEV = forced expiratory volume; FVC = forced vital capacity; KL-6 = Krabs von den Lungen-6; LDH = lactate dehydrogenase; RF = rheumatoid factor; SP-D = surfactant protein-D; TP = total protein; VC = vital capacity; γ-GTP =γ-glutamyl transpeptidase.