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【 CASE REPORT 】

Anti-EJ Antibody-positive Anti-synthetase Syndrome Associated with Retroperitoneal Sarcoma

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Abstract:
A 74-year-old man with interstitial lung disease (ILD) underwent surgical excision of a growing retroperitoneal tumor and was diagnosed with spindle cell sarcoma. Just after the surgery, skin eruption and muscle weakness emerged. Based on his symptoms and examination findings, we diagnosed him with anti-synthetase syndrome (ASS) with positive anti-glycyl-transfer ribonucleic acid synthetase antibody (anti-EJ) as paraneoplastic syndrome. Immunosuppressive treatments kept his progressing ILD stable for 21 months, although an expanding lung metastatic lesion from primary sarcoma was detected. Measurements of myositis-specific antibodies may enable the prediction of the efficacy of immunosuppressive treatments for paraneoplastic syndrome, even if the primary disease becomes progressive.

Key words: anti-synthetase syndrome (ASS), anti-EJ antibody, sarcoma, dermatomyositis (DM), paraneoplastic syndrome

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Introduction

Dermatomyositis (DM) is an idiopathic inflammatory myopathy characterized by proximal skeletal muscle weakness and characteristic skin rash. Previous reports have shown an association between DM and malignancies, including ovarian, lung, breast, nasopharyngeal, pancreatic, stomach, and colorectal cancer as well as malignant lymphoma (1, 2). Serum autoantibodies in DM can indicate a positive or negative risk of malignancy; indeed, antibodies to transcription intermediary factor (TIF)-1 gamma and nuclear matrix protein (NPX)-2 indicate positive risks, while anti-synthetase antibodies, anti-Mi-2 antibody, and anti-signal recognition particle (SRP) antibody indicate negative risks (3).

Anti-synthetase syndrome (ASS) is characterized by the presence of anti-aminoacyl tRNA synthetase (anti-ARS) autoantibodies and clinical symptoms of myositis (frequency: 78-91%), interstitial lung disease (ILD) (90%), Raynaud's phenomenon (62%), arthritis (64-83%), a fever (20%), and mechanic's hands (17-71%) (4).

Aminoacyl-tRNA synthetases are enzymes that catalyze the binding of amino acids to their corresponding tRNAs. Antibodies to eight different tRNA synthetase have been reported: anti-histidyl (Jo-1), threonyl (PL-7), alanyl (PL-12), glycyl (EJ), isoleucyl (OJ), asparaginyl (KS), phenylalanyl (Zo), and tyrosyl (YRS) tRNA synthetase antibodies (5). Anti-ARS antibodies except for anti-Jo-1 antibody are usually found in <5% of polymyositis and dermatomyositis (PM/DM) patients (6).

We herein report the first case of anti-EJ antibody-positive ASS associated with retroperitoneal sarcoma despite ASS being uncommon as a phenotype of paraneoplastic syndrome and sarcoma exceptional as the cause of paraneoplastic syndrome.

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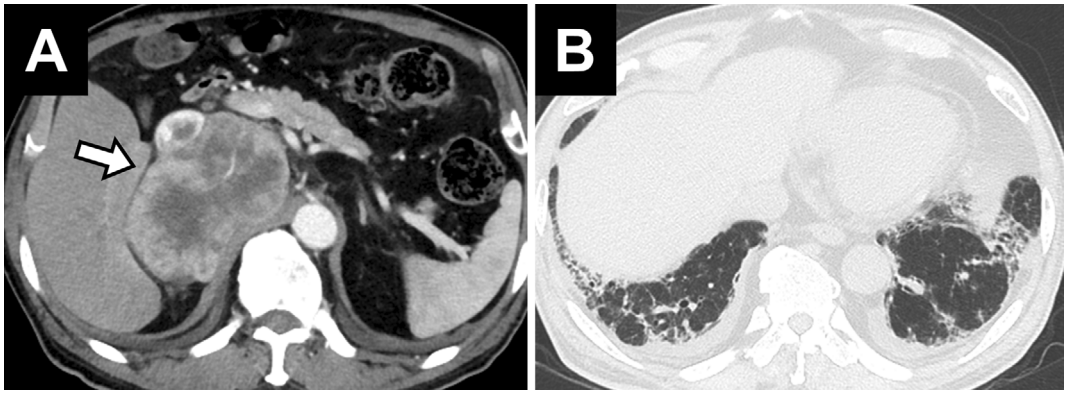

Figure 1. **(A) The white arrow indicates the retroperitoneal tumor. (B) The interstitial lung disease (ILD) before the operation.**

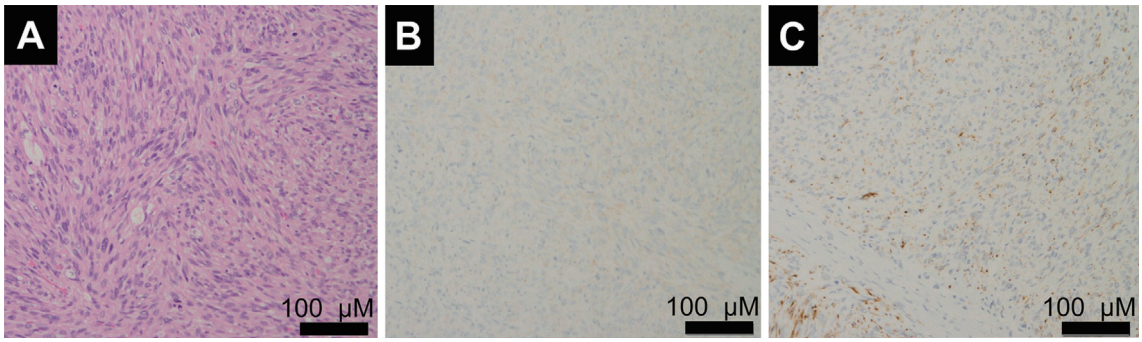

Figure 2. **Histopathological findings of the sarcoma in the patient. (A) Hematoxylin and Eosin staining: the tumor comprised high-cellularity areas with a prominent spindle-cell pattern arranged in a fascicular architecture. (B) S100 and (C) desmine stainings were focally positive.**

Case Report

A 74-year-old man presented with intermittent pain in the right upper abdominal quadrant and back for several months. He had also developed temporal itchy rashes in the abdomen around the same period. Computed tomography (CT) revealed a solid lobulated tumor 10 cm in diameter above the superior pole of the right kidney and behind the inferior vena cava (Fig. 1A). Chest CT showed findings of ILD mainly in the lower lobes of both of lungs (Fig. 1B). This case was considered a possible malignant retroperitoneal tumor, and he was admitted to our hospital for surgical treatment.

After confirming that his cardiac and pulmonary function were sufficient to tolerate surgery, retroperitoneal tumor resection was performed. He was diagnosed with undifferentiated spindle cell sarcoma pathologically. The tumor comprised high-cellularity areas with a prominent spindle-cell pattern arranged in a fascicular architecture. Most of the tumor cells had tapering nuclei, and some had eosinophilic cytoplasm (Fig. 2A). Immunohistochemistry showed no specific reproducible immunophenotype. Immunostaining by S100 (Fig. 2B), CD56, and desmin (Fig. 2C) was focally positive, and staining using the following antibodies was negative: chromogranin A, synaptophysin, alpha-smooth muscle actin, CAM5.2, AE1/AE3, c-kit, CD34, inhibin, CD68, MDM2, and CDK4.

Although the postoperative course was uneventful, he started to complain of itchy erythematous papules on his back and slight muscle weakness of the lower limbs. According to his strong desire to be discharged, several additional examinations were planned in an outpatient setting. Two months later, his skin symptoms were found to have persisted, and muscle weakness had emerged. He was therefore hospitalized for a further examination and treatment.

The patient had no remarkable medical history but had had a habit of smoking 20 cigarettes a day for 35 years from 20 to 55 years old. His family history included a sister with rheumatic disease whose details were unknown.

On a physical examination, auscultation of the chest showed fine crackles in the right lower lung field dominantly and no heart murmur. He presented with Shawl sign (Fig. 3A), V-neck sign (Fig. 3B), Gottron's sign (Fig. 3C, D-1, D-2), mechanic's hands (Fig. 3E), and erythema with scales on his abdomen and back. Manual muscle testing (MMT) for the proximal lower limb was grade 4, although other muscle groups showed grade 5 results. Pulmonary function tests showed a vital capacity (VC) of 1.94 L (58.3% of the predicted value), forced vital capac-

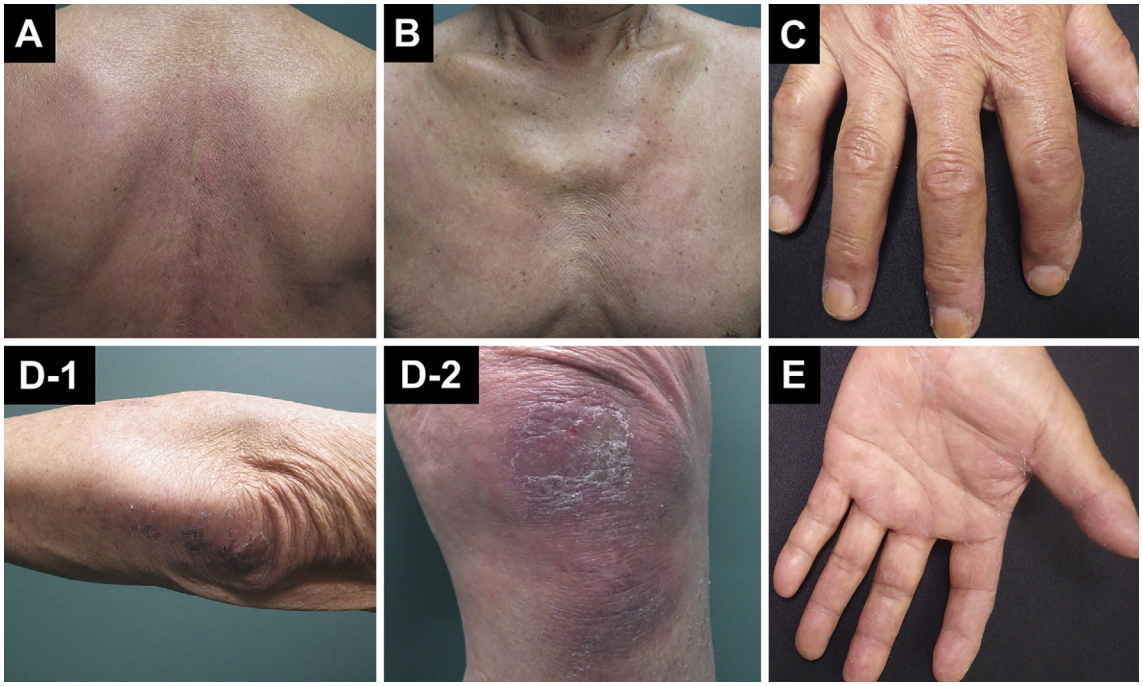

Figure 3. **Skin eruption of the patient. (A) Shawl-sign. (B) V-neck sign. (C, D-1, D-2) Gottron's sign. (E) Mechanic's hands.**

Table. **Results of the Patient's Laboratory Tests.**

	Normal	Result	Unit		Normal	Result	Unit
WBC	3,500-9,100	13,600	/μL	Cr	0.46-0.79	0.65	mg/dL
Seg	40-60	79.9	%	AST	13-30	73	IU/L
Lym	25-50	10.1	%	ALT	7-23	60	IU/L
Mo	1-14	4.5	%	LDH	124-222	516	U/L
Eos	0-5	5.2	%	GGT	13-64	16	U/L
Baso	0-2	0.3	%	CK	59-248	1,972	U/L
Hb	11.6-14.8	12.9	g/dL	CH50	30-46	50.5	U/mL
Plt	158-348	257	$\times 10^3/\mu L$	ALD	2.7-7.5	45.4	U/L
CRP	0.00-0.14	2.47	mg/dL	KL-6	<500	504	U/mL

WBC: white blood cell count, Seg: segmented neutrophils, Lym: lymphocytes, Mono: monocytes, Eo: eosinophils, Baso: basophils, Hb: hemoglobin, Plt: platelet count, CRP: C-reactive protein, Cr: serum creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, LDH: lactate dehydrogenase, GGT: gamma-glutamyltransferase, CK: creatine kinase, CH50: total hemolytic complement, ALD: aldolase, KL-6: Krebs von den Lungen-6

ity (FVC) of 1.89 L (56.8% of the predicted value), forced expiratory volume in 1 second (FEV_1) of 1.46 L (59.8% of the predicted value), and diffusing capacity of the lung for carbon monoxide (DL_{CO}) of 6.09 mL/min/mmHg (34.8% of the predicted value). The preoperative values were as follows: VC 2.80 L (83.8% of the predicted value), FVC 2.90 L (86.8% of the predicted value), and FEV_1 2.17 L (87.9% of the predicted value). During a 6-minute walk test, desaturation to 84% was observed.

The Table shows his laboratory examination results. The serum autoantibodies were as follows: antinuclear antibody was negative; anti-glycyl-transfer ribonucleic acid synthetase antibody (anti-EJ) was positive; other ARS antibodies, anti-melanoma differentiation-associated gene 5 (MDA5) antibody, and anti-transcriptional intermediary factor 1-γ (TIF1-γ) antibody were negative; and both myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA) and proteinase 3-antineutrophil cytoplasmic antibody (PR3-ANCA) were <1.0 U/mL (normal range ≤3.5 U/mL). Anti-ARS antibodies were detected at Nippon Medical School by an RNA immunoprecipitation assay using K562-cell extracts as described previously (7). The anti-EJ antibody result was judged to be positive when the given serum sample precipitated RNA components identical to those precipitated by the prototype sera positive for anti-EJ.

Electromyography showed mild myogenic changes of the proximal muscle, including polyphasic motor unit potentials. Chest CT revealed pleural effusion, predominantly basal

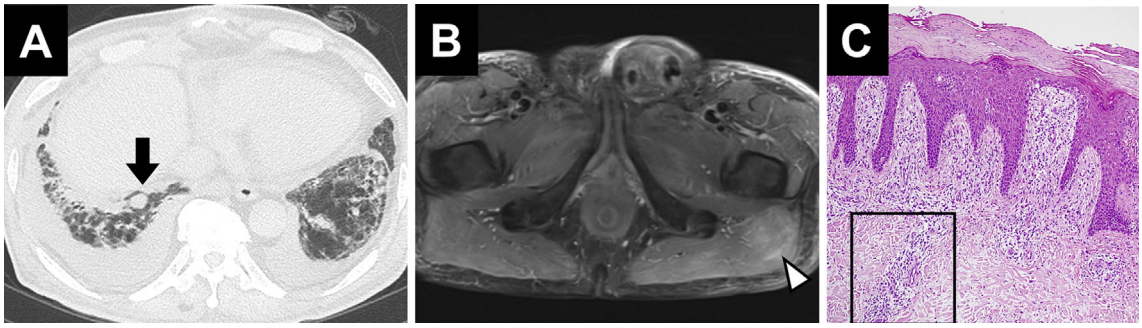

Figure 4. **(A) Two months after the operation. The pleural effusion and ILD were worsening, and the black arrow indicates a small nodular shadow in the right lower lobe. (B) The white arrowhead indicates the diffuse high-intensity-signal areas in his lumbar region on T2-weighted imaging with fat suppression. (C) Hematoxylin and Eosin staining, 40×: a skin biopsy showed infiltration of lymphocytes and eosinophils in the edematous region around blood vessels in the dermis layer (black square). ILD: interstitial lung disease**

ground-glass opacity, and a reticular pattern, i.e. a nonspecific interstitial pneumonia (NSIP) pattern, along with a small nodular shadow in the right lower lobe (Fig. 4A). We decided to monitor the size of the nodule because it was suspected to be a metastasis of sarcoma. Magnetic resonance imaging (MRI) showed high intensities on the fascia of the gluteus maximus muscle and diffuse high intensities in the muscles from the lumbar region to the thigh and lower legs (Fig. 4B). A skin biopsy from the keratinized skin with erythema under the knee showed infiltration of lymphocytes and eosinophils in the edematous region around blood vessels in the dermis layer (Fig. 4C), although a muscle biopsy was not performed because the patient withheld his consent.

This patient was diagnosed with anti-synthetase syndrome because of the positive anti-EJ antibody. Furthermore, his clinical findings fulfilled the Bohan and Peter criteria for DM (8, 9) because of the symmetrical proximal muscle weakness, the elevation in serum skeletal muscle enzymes, the electromyogram pattern of myositis and the typical rash of DM. According to the 2017 European League Against Rheumatism/American College of Rheumatology (EULAR/ACR) classification criteria for idiopathic inflammatory myopathies (IIM) (10), the score without a muscle biopsy was 8.4, the probability was 96%, the classification was definite IIM, and the subgroup was DM.

Prednisolone 70 mg/day (1 mg/kg body weight/day) was initiated, and methylprednisolone pulse therapy and administration of tacrolimus 2 mg/day were started because a sufficient decrease in the levels of muscle enzymes was not achieved. A month later, his subjective symptoms of itchy erythematous papules and muscle weakness were improved. Grade 4 muscle weakness of the proximal lower limb improved to grade 5. The creatine kinase level normalized to 61 U/L. Pleural effusion was found to have decreased on CT; however, the pulmonary solitary nodule had increased in size, and pulmonary metastasis was suspected. We referred him to the Department of Thoracic Surgery. He was discharged on prednisolone 40 mg/day and tacrolimus 4 mg/day, and resection of the lung metastasis was considered.

Three months after the immunosuppressive treatment was started, preoperative examinations were performed. Pulmonary function test findings were improved as follows: VC was 2.54 L (76.5% of the predicted value), FVC was 2.52 L (75.9% of the predicted value), FEV_1 was 1.94 L (80.2% of the predicted value) and DL_{CO} was 9.85 mL/min/mmHg (62.1% of the predicted value). However, CT revealed that the pulmonary nodule had grown to 20 mm in diameter (Fig. 5A-1), right pleural effusion had increased, and nodular right pleural thickening had emerged (Fig. 5A-2). These lesions showed an increased fluorodeoxyglucose uptake on fluorodeoxyglucose positron emission tomography (FDG-PET) (Fig. 5B-1, B-2). Surgical resection was canceled, and we started treatment with doxorubicin for the lung metastasis and the pleural dissemination of the retroperitoneal sarcoma. However, because ILD temporarily worsened (Fig. 6) and neutropenia of grade 4 according to the Common Terminology Criteria for Adverse Events (CTCAE), version 5.0, emerged after the administration of doxorubicin, we considered continuing chemotherapy for sarcoma to be difficult and therefore discontinued it. The dose of prednisolone was also tapered.

He has been followed for 21 months since the surgery without progression of ILD or dyspnea using prednisolone and tacrolimus, although the metastatic lesion has been growing.

Discussion

We herein report the first case of anti-EJ antibody-positive ASS associated with sarcoma. We assumed that sarcoma had induced anti-EJ antibody-positive ASS as paraneoplastic syndrome for two reasons. First, sarcoma emerged within five years of the diagnosis of ASS, which also met the classification criteria of DM. Our case met the recommended diagnostic criteria for paraneoplastic neurological syndrome (PNS) as definite PNS (11). The onset of ILD was unknown

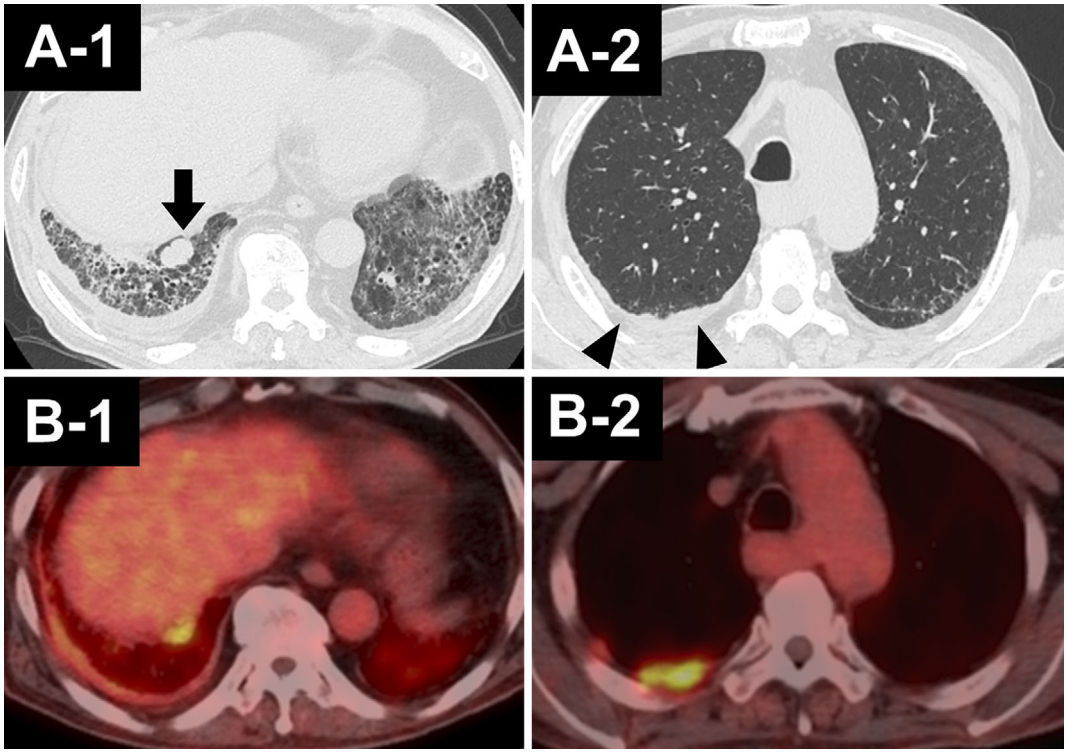

Figure 5. **Two months after treatment for the ASS was started, the pulmonary nodule had grown (black arrow in A-1), the right pleural effusion had increased, and nodular right pleural thickening had emerged (black arrowheads in A-2). These lesions showed an increased fluorodeoxyglucose uptake on fluorodeoxyglucose positron emission tomography (FDG-PET) in B-1 and B-2. ASS: antisynthetase syndrome**

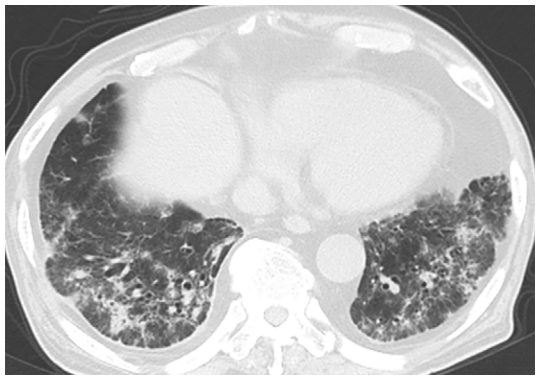

Figure 6. **ILD worsened after the administration of doxorubicin. ILD: interstitial lung disease**

and may have been earlier than that of sarcoma because it seemed to have some chronic components, such as fibrosis. However, ASS still might have been PNS because subjective skin symptoms appeared at the same time as the development of sarcoma, and the exacerbation of ILD may have been related to the progression of metastases. Although the symptoms of PNS are generally expected to improve after cancer treatment, the skin and musculoskeletal symptoms of the present patient did not show any significant improvement after tumor resection. Therefore, we speculate that resident metastatic tumor cells which already existed enabled the anti-tumor lymphocytes to continue to act as autoreactive lymphocytes. Second, both retroperitoneal sarcoma and ASS are rare diseases; the average annual incidence of retroperitoneal sarcoma and all types of DM was approximately 2.7 cases (12) and 10 cases (13) per million population, respectively. The likelihood that both of these rare conditions occurred independently is extremely low.

DM associated with sarcoma has been previously reported (14-16), but no information on anti-ARS antibodies aside from anti-Jo-1 antibody has been described. Anti-ARS autoantibodies are identified in patients with cancer-associated myositis (13%) (17). A study of the clinical features of ASS (18) reported that only 1 of 38 cases of anti-EJ antibody-positive ASS had malignancy (nasopharyngeal cancer). Sarcoma is not regarded as a common cause of myositis. To our knowledge, this is the first reported case of anti-EJ antibody-positive ASS associated with sarcoma.

The detection of anti-ARS antibodies may be useful for deciding treatments for ILD and predicting the effectiveness, as ILD in cases of anti-EJ antibody-positive ASS has shown a good response to initial treatment (19) but also a high rate of relapse, especially in cases of acute-onset ILD with corticosteroid monotherapy (20). The combination therapy of corticosteroid and immunosuppressant administered to the present patient was also effective against ILD. Furthermore, the detection of anti-ARS antibodies may predict the prognosis of patients. Patients with anti-EJ antibody-positive ASS show a poorer prognosis than those with anti-Jo-1

antibody-positive ASS (21). In addition, our patient also had poor prognostic factors of PM/DM, including an age over 64 years old, male gender, non-Caucasian race, and a complication of malignancy (2). Based on this evidence, our patient is assumed to have a poor prognosis. However, even if patients who have ASS with malignancy that is not able to be resected completely or receive effective chemotherapy, immunosuppressive therapy may maintain the symptom-free period and improve the quality of life, even after considering the adverse effects of immunosuppressant therapy.

The present patient remained free from the symptoms of ILD due to the use of corticosteroid and tacrolimus, and his malignancy became a critical component influencing his prognosis. The overall median survival from the diagnosis of pulmonary metastasis for patients with soft tissue sarcoma is 15 months, and the 3-year survival rate is 25% (22). Improving and maintaining the quality of life in this period is important because our patient actually has been alive without dyspnea for 21 months.

We reported the first case of anti-EJ antibody-positive ASS associated with the emergence of retroperitoneal sarcoma. In patients who have malignancy accompanied by ILD, the presence of musculoskeletal manifestations and carefully measuring the myositis-specific autoantibodies (MSAs) may be useful for identifying the existence of paraneoplastic syndrome. MSAs may also help predict the disease prognosis of patients with paraneoplastic syndrome as well as to determine whether or not immunosuppressive therapy should be added to the anti-tumor therapy regimen.

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

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