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

Saeko Fukui¹, Kazuma Kobayashi¹, Yuya Fujita², Shoichi Fukui², Naoki Iwamoto², Tomohiko Adachi¹, Masaaki Hidaka¹, Mitsuhisa Takatsuki¹, Kuniko Abe³, Masataka Kuwana⁴, Atsushi Kawakami² and Susumu Eguchi¹

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.

¹Department of Surgery, Nagasaki University Graduate School of Biomedical Science, Japan, ²Department of Immunology and Rheumatology, Nagasaki University Hospital, Japan, ³Department of Pathology, Nagasaki University Hospital, Japan and ⁴Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, Japan

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Correspondence to Dr. Kazuma Kobayashi, kazuma-k2013@nagasaki-u.ac.jp
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 ×10^3/μL | 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, Mo: monocytes, Eos: 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

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

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 FEV1 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
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), FEV1 was 1.94 L (80.2% of the predicted value) and DLCO 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...
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
The authors state that they have no Conflict of Interest (COI).

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