

[ CASE REPORT ]

## Small Cell Lung Cancer Patient with Anti-transcriptional Intermediary Factor 1 $\gamma$ Antibody Who Developed Dermatomyositis after Successful Chemoradiotherapy

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### Abstract:

We herein report a 63-year-old woman with small-cell lung cancer (SCLC) who developed dermatomyositis (DM) after initial chemoradiotherapy despite tumor reduction. Serum anti-transcriptional intermediary factor (TIF) 1 $\gamma$  antibody was detected before the development of DM, and its levels increased over time. She died five months after the diagnosis of SCLC. Anti-TIF1 $\gamma$  antibody is known to be a marker for cancer-associated DM (CAM); however, the present case indicates that the antibody can be found in cancer patients without DM. This case is also unusual, as DM developed later despite successful chemoradiotherapy.

**Key words:** anti-transcriptional intermediary factor 1  $\gamma$  antibody, chemoradiotherapy, dermatomyositis, autoantibody, small-cell lung cancer

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### Introduction

Dermatomyositis (DM) and polymyositis (PM) are systemic autoimmune rheumatic diseases characterized by proximal muscle weakness, myalgia, and characteristic skin rash. An increased risk of cancer in DM/PM, particularly DM, has been well described for many years. In recent years, anti-transcriptional intermediary factor 1  $\gamma$  (TIF1 $\gamma$ ) antibody was shown to be strongly associated with cancer-associated DM/PM (CAM), as confirmed by a meta-analysis (1-4).

We herein report a rare case of small-cell lung cancer (SCLC) in which anti-TIF1 $\gamma$  antibody was detected prior to the appearance of DM. The patient developed muscle weakness, elevated muscle enzymes, and typical skin rash of DM after initial chemoradiotherapy for SCLC despite tumor reduction.

### Case Report

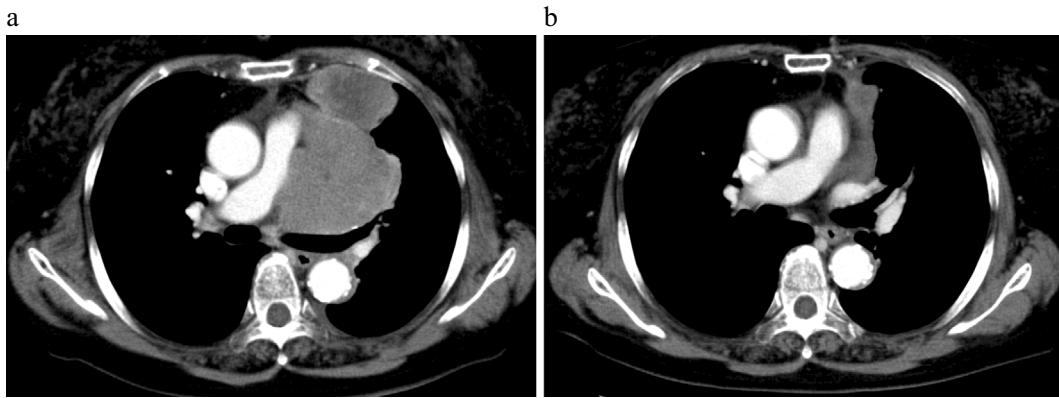
A 63-year-old woman with a smoking history of 20 pack-years, alcoholic liver injury, and hypertension had onset of cough and hoarseness.

A chest X-ray showed left hilar enlargement, and chest computed tomography (CT) revealed a 5-cm mass in the left upper lobe and 8-cm diameter mediastinal lymph node swelling (Fig. 1a). The levels of serum tumor markers, such as pro-gastrin-releasing peptide (pro-GRP) (4,490 pg/mL; normal range, <46 pg/mL) and nerve-specific enolase (NSE) (138 ng/mL; normal range, <10 ng/mL), were elevated. The serum levels of aspartate transferase (35 IU/L) and creatine kinase (57 U/L) were within normal limits, while those of lactate dehydrogenase (286 IU/L) and C-reactive protein (0.57 mg/dL) were slightly increased. Pathology of biopsy specimens obtained from the mediastinal lymph node and left main tumor by flexible bronchoscopy revealed SCLC,

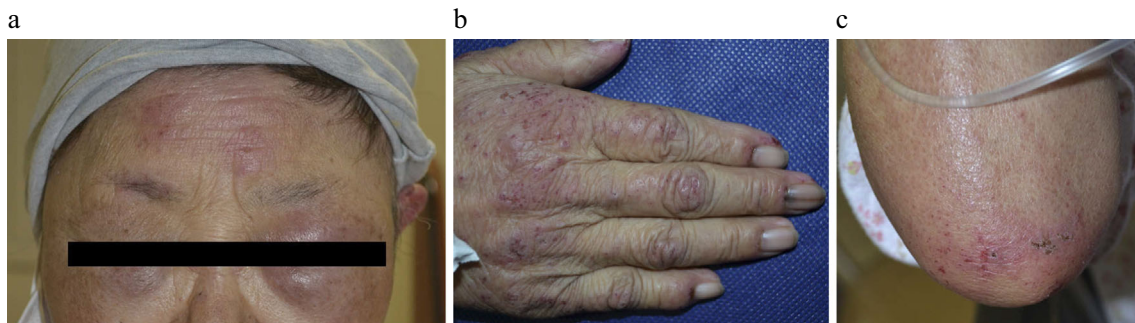
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**Figure 1.** Computed tomography (CT) image of the chest. CT at the initial admission showing a mass in the left upper lobe (5 cm in diameter) and a mediastinal lymph node (8 cm in diameter) (a), and CT five weeks after chemoradiotherapy showing reductions in the size of the lung and mediastinal lymph node masses (b).



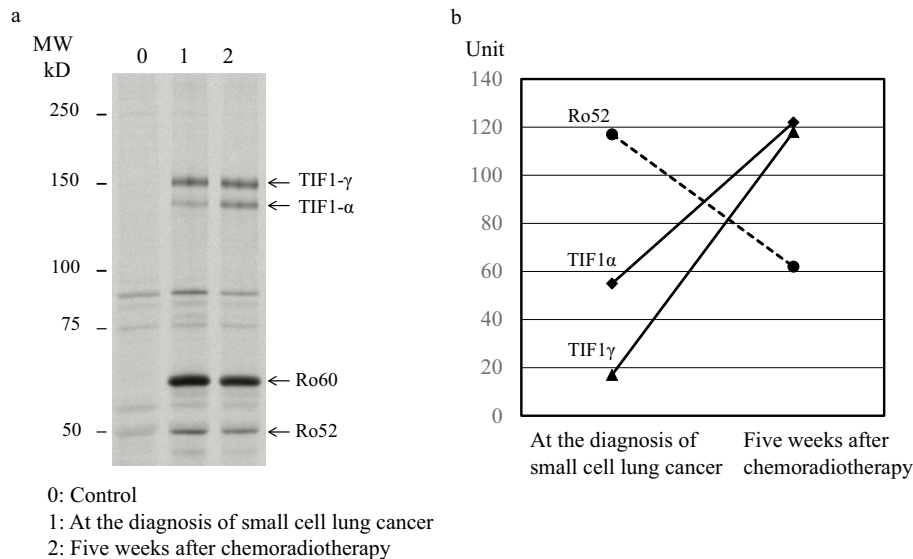
**Figure 2.** Cutaneous findings upon admission. Heliotrope (a), nail-bed bleeding (b), and Gottron's sign (b) (c) were observed.

and a systemic image analysis showed no distant metastasis; thus, she was diagnosed with limited stage SCLC. Systemic chemoradiotherapy with carboplatin plus etoposide was initiated, which led to a significant reduction in the tumor size in the lung and mediastinal lymph node on chest X-ray and a decrease in the levels of serum tumor markers. She was discharged without any clinical signs or symptoms of PM/DM at 27 days after chemotherapy. However, a week later, general malaise; facial edema; erythema on the hand, back, and body; proximal myalgia; muscle weakness; and dysphagia developed, and she was urgently readmitted to our hospital.

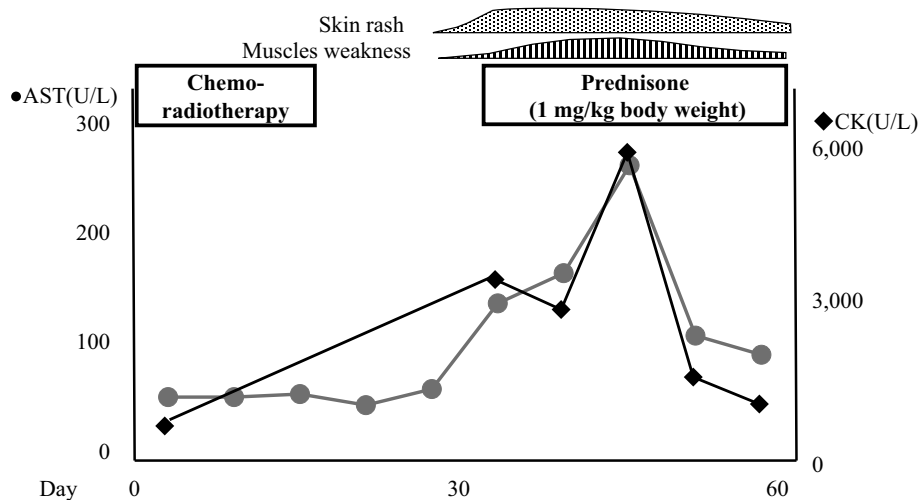
At the time of readmission, she was alert, and physical findings were as follows: height 146.5 cm, body weight 47.5 kg, body temperature 36.9 °C, blood pressure 134/85 mmHg, pulse rate 108 beats/min, and respiratory rate 17 cycles/min. The Eastern Cooperative Oncology Group Performance Status (ECOG-PS) was grade 4. Breathing and heart sounds were normal. Upon an examination, erythema on the face; heliotrope rash; aphthous ulcer in the oral cavity; extensive edematous erythema in the neck extending to the chest, back, and belt line; nail-bed bleeding; and Gottron papule were observed (Fig. 2). Muscle grasping pain was noted in both upper arms and thighs. Muscle weakness in

the proximal muscles of the upper and lower limbs was also observed, and the results of a manual muscle test of the bilateral pectoralis major muscles, deltoid muscle, triceps brachii, iliopsoas, quadriceps muscle, and hamstrings were 4 of 5.

The serum levels of myogenic enzymes were elevated (aspartate transferase, 166 IU/L; lactate dehydrogenase, 486 IU/L; creatine kinase, 3,272 U/L; aldolase, 15.2 U/L; myoglobin, 1,854 ng/mL). The serum C-reactive protein levels (1.59 mg/dL) and blood sedimentation rate (71 mm/h) were elevated. The tumor marker levels were decreased compared with those at the time of the diagnosis (pro-GRP, 62.8 pg/mL; NSE, 30.9 ng/mL). Chest CT showed a marked reduction in the tumor size in the lung and mediastinal lymph node (Fig. 1b). Antinuclear antibodies were positive, with a titer of 1:640 in speckled and cytoplasmic patterns. Serum autoantibodies were evaluated according to immunoprecipitation and enzyme-linked immunosorbent assays, as described previously (5). Anti-TIF1 $\gamma/\alpha$ , anti-Ro60, and anti-Ro52 antibodies were positive at the diagnosis of SCLC before the development of DM and chemoradiotherapy (Fig. 3). The levels of anti-TIF1 $\gamma/\alpha$  antibodies increased by 2- to 6-fold after the onset of DM, whereas those of anti-Ro52 antibodies decreased (Fig. 3b). Antibodies to aminoacyl-



**Figure 3.** An analysis of autoantibodies. (a) Immunoprecipitation. Autoantibodies in the sera were tested using  $^{35}\text{S}$ -methionine labeled K562 cell lysate. Anti-transcriptional intermediary factor 1 $\gamma/\alpha$  (anti-TIF1- $\gamma/\alpha$ ) and Ro60 antibodies were positive at the diagnosis of small-cell lung cancer and five weeks after chemoradiotherapy when dermatomyositis developed. Although a protein band of approximately 50 kD was noted, Ro52 could not be clearly seen in this condition. (b) ELISA. Levels of autoantibodies to TIF1- $\gamma/\alpha$  and Ro52 by ELISA at the diagnosis of lung cancer and five weeks after chemoradiotherapy are shown. Anti-Ro60 was negative on ELISA.



**Figure 4.** Clinical course.

tRNA synthetases and -Mi-2 were negative. She was diagnosed with classic DM based on muscle weakness, elevated levels of muscle enzymes, and typical skin rash. In addition, CAM was diagnosed because of the evidence of SCLC with positive results for anti-TIF1 $\gamma$  antibody (6). Although anti-Ro60 and anti-Ro52 antibodies were positive, she did not have sicca symptoms of Sjögren's syndrome.

High-dose corticosteroid therapy (prednisone 1 mg/kg body weight) was initiated for DM, resulting in only partial improvement in muscle and skin symptoms (Fig. 4). Her general condition and performance status did not improve because of complicating bacterial pneumonia, a worsened

mental condition, and SCLC progression. Thus, additional systemic chemotherapy could not be administered, and she died five months after the diagnosis of SCLC at another hospital where she had been transferred for terminal care.

## Discussion

We herein report a rare case of CAM that developed after initial chemoradiotherapy for SCLC despite tumor reduction. Serum anti-TIF1 $\gamma$  antibody was detected when the diagnosis of SCLC was made before the treatment of cancer and the development of DM, and its levels increased over time.

In patients with CAM, the occurrence of DM/PM after the diagnosis of malignant tumors is not rare (2, 7-9). Indeed, one study reported that more than 30% of malignancies preceded the diagnosis of DM/PM (7). Regarding the association between the cancer and activity of DM/PM, successful treatment of cancer, typically removal of cancer by surgery, leads to an improvement of the activity of DM/PM, and the relapse of cancers usually lead to flare-up of DM/PM (10-13). Given previous findings, the present case appears to be a very rare one because CAM developed after a marked reduction in tumor size by chemoradiotherapy and anti-TIF1 $\gamma$  antibodies were detected in a patient with SCLC without any signs of DM/PM.

The mechanism through which CAM developed after initial chemoradiotherapy for SCLC despite tumor reduction with increased levels of TIF1 $\gamma$  antibody in our patient is unclear. Since *TIF1* is a known tumor-suppressor gene, a mutation in *TIF1* may have been the primary event, leading to the development of SCLC, with mutated TIF1 antigens inducing an autoimmune response (4). Abnormal proteins expressed by tumor tissues may lead to an immune response, and the expression of mutated antigens may lead to the production of specific autoantibodies, such as anti-p53 and RNA polymerase III antibodies (14, 15). Furthermore, a large amount of tumor antigens released during chemoradiotherapy might play a role in stimulating the immune system, accelerating the autoantibody production and the subsequent development of DM in the present case. However, our speculation cannot be definitively confirmed, and the development of DM in this case might simply be a natural course.

Another interesting point of this case is the detection of anti-TIF1 $\gamma$  antibody at the cancer diagnosis before the onset of DM. The detection of anti-TIF1 $\gamma$  antibody in patients with malignancy without DM has not been well documented; only three cases of borderline positivity of the antibody in breast cancer patients without rheumatic diseases have been reported (16). The present case suggests that the detection of anti-TIF1 $\gamma$  antibody in cancer patients may be a useful marker for predicting DM/PM onset. Of further note, the levels of anti-Ro52 antibodies decreased while those of anti-TIF1 $\gamma$  and anti-TIF1 $\alpha$  increased by 2- to 6-fold during the development of DM (Fig. 3b). Some autoantibodies may share common mechanisms of regulation, although non-parallel changes in different specific autoantibodies have also been reported. The development of anti-U1RNP or ribosomal P antibodies and a reduction in anti-RNA helicase A antibody levels in SLE has been reported (17). Our data therefore suggest different mechanisms of regulation for anti-TIF1 $\gamma$  and anti-TIF1 $\alpha$  antibodies and for anti-Ro52 autoantibodies.

In the present case, anti-TIF1 $\gamma$  and anti-TIF1 $\alpha$  antibodies were both positive. Fujimoto et al. showed that anti-TIF1 $\alpha$  antibody often coexists with anti-TIF1 $\gamma$  antibody (18). Another report demonstrated that anti-TIF1 $\alpha$  antibody can be found in patients with anti-Mi-2 antibody but without anti-

TIF1 $\gamma$  antibody. In the present case, anti-Mi-2 antibody was negative, and cases with both anti-TIF1 $\gamma$  and TIF1 $\alpha$  antibodies developed cancer more frequently than those with only anti-TIF1 $\alpha$  antibodies (19). However, the clinical significance of these antibodies in lung cancer patients is not well understood, and the accumulation of more cases is desired.

The prognosis of patients with CAM generally depends on the prognosis of cancer (20-23); therefore, the treatment of cancer is essential for CAM. Treatment with corticosteroids and/or immunosuppressants is considered when necessary. In a review of 12 patients with CAM with SCLC, a very poor prognosis of 2 weeks to 9 months (median: 5 weeks) was reported (24). Compared with the median survival of 9.4 to 12.8 months in patients with extensive-disease SCLC, the prognosis of SCLC patients with CAM may be worse than that in patients with SCLC without CAM (25). An inadequate response of myopathy to corticosteroid treatment in certain patients may limit the treatment options for cancer, as seen in our case, leading to a poor prognosis.

### Conclusion

We herein report a rare case of SCLC with anti-TIF1 $\gamma$  antibody and the subsequent development of DM despite tumor reduction by systemic chemoradiotherapy along with an increase in the levels of anti-TIF1 $\gamma$  antibody. Anti-TIF1 $\gamma$  antibody is known to be a marker for CAM; however, the present case indicates that the antibody can be found in cancer patients without DM. It should be noted that CAM might be a poor prognostic factor for SCLC.

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

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