Small cell lung cancer and interstitial pneumonia associated with anti-transcriptional intermediary factor-1γ-positive dermatomyositis

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Keywords
Dermatomyositis, interstitial lung disease, lung cancer, malignancy, transcriptional intermediary factor-1γ.

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Abstract
Antibodies to transcriptional intermediary factor-1γ (TIF-1γ) are strongly associated with malignancy in patients with dermatomyositis but a relatively low risk for interstitial lung disease. We report the case of a 68-year-old female with small cell lung cancer (SCLC) and interstitial pneumonia who was diagnosed first with dermatomyositis positive for serum anti-TIF-1γ antibodies. Because interstitial pneumonia co-existed, she was treated with carboplatin and etoposide without radiotherapy. A significant improvement in skin disease and SCLC was seen in response to chemotherapy. The levels of anti-TIF-1γ antibodies were also decreased by chemotherapy. Her interstitial pneumonia was mild with normal pulmonary function and did not change during the observation period. This is the first report of dermatomyositis associated with anti-TIF-1γ antibodies co-existing with interstitial pneumonia and SCLC. Because cases with interstitial pneumonia in cancer-associated dermatomyositis positive for anti-TIF-1γ antibodies are few in number, further studies are necessary to elucidate the clinical features.

Introduction
Dermatomyositis is one of the autoimmune diseases characterized by muscle weakness, skin diseases, and internal organ involvement such as interstitial lung disease (ILD) and malignancy [1]. There is clinical evidence that autoantibodies against transcriptional intermediary factor-1γ (TIF-1γ), also known as p155 protein, are associated with malignancy, including lung cancer, in patients with dermatomyositis [2–4]. Several myositis-related autoantibodies such as antibodies to aminoacyl-transfer RNA synthetase (ARS) and melanoma differentiation associated protein 5 (MDA5) are associated with ILD [1]. In contrast, dermatomyositis patients positive for anti-TIF-1γ antibodies rarely exhibit ILD [1]. Here, we describe a case of TIF-1γ-positive dermatomyositis co-existing with small cell lung cancer (SCLC) and ILD.

Case Report
A 68-year-old female who had a smoking history was referred to the Department of Dermatology, Aichi Medical University, because she presented with an erythematous skin rash lasting for three months. Physical examination showed skin signs such as Gottron’s sign, V-neck sign, and mechanic’s hand (Fig. 1A–C) and fine crackles at the bilateral lung bases without obvious muscle weakness. The serum levels of myogenic enzymes, creatine kinase (252 U/L), myoglobin (141 ng/mL), aspartate aminotransferase (40 U/L), lactate dehydrogenase (309 U/L), and a marker of ILD, Krebs von den Lungen-6 (676 U/mL), were elevated. Anti-nuclear antibodies were positive at a titre of 1:40 in a speckled pattern. Examinations of autoantibodies were positive for anti-TIF-1γ antibodies (102 U, cut-off value < 32 U) but negative for other dermatomyositis-
related autoantibodies (Jo-1, ARS, Mi-2, and MDA5), anti-SS-A, anti-SS-B, and anti-double stranded DNA antibodies. Histopathology of a skin biopsy from the Gottron’s sign lesion showed superficial dermal oedema with perivascular lymphocytic infiltration and mild collagen fibre swelling and focal mucin deposition in the dermis (Fig. 1D). These findings were compatible with dermatomyositis. Systemic computer tomography (CT) searching for a co-existent malignancy showed a lung nodule of the right lower lobe, right hilar lymphadenopathy, reticular shadow of the bilateral lower lobes, and mild diffuse emphysematous changes (Fig. 2A). CT findings of interstitial pneumonia features included honeycombing and traction bronchiectasis with the concurrent presence of ground grass opacification and reticulation (Fig. 2A), suggesting the usual interstitial pneumonia pattern.

She was referred to the Department of Respiratory Medicine and Allergology, where a transbronchial biopsy using a flexible bronchoscope was performed. The nodule of the right lung exhibited SCLC. Images of 18F-FDG-positron emission tomography/CT showed uptake of 18F-FDG in the lung nodule and lymphadenopathy (Fig. 2B). Tumour marker tests revealed an elevated level of serum pro-gastrin-releasing peptide (204 pg/mL). Pulmonary function test results showed normal levels of forced vital capacity (110% of predicted), forced expiratory volume in one second (103% of predicted), and diffusion capacity of the lung for carbon monoxide (105% of predicted). Finally, she was diagnosed with SCLC of clinical T1N2M0 stage IIIA. Because interstitial pneumonia co-existed, she received systemic chemotherapy with carboplatin and etoposide for six cycles without radiotherapy. The chemotherapy was effective not only for SCLC but also for the skin symptoms. Three months after the final first-line chemotherapy, she started amrubicin as the second-line regimen due to regrowth of the primary lung tumour. Her skin symptoms remained stable even when her SCLC regrew. The amrubicin therapy was effective for her SCLC. The levels of anti-TIF-1γ antibodies after five and seven cycles of chemotherapy with amrubicin were 45 and 15 U,
respectively. There was no change in interstitial pneumo-
nia during the observation period. No systemic corticoste-
roid or immunosuppressant was used for the treatment of
dermatomyositis or interstitial pneumonia.

Discussion

To our knowledge, this is the first report of a patient with
dermatomyositis positive for anti-TIF-1γ antibodies com-
plicated by SCLC and interstitial pneumonia. Anti-TIF-1γ
antibodies are strongly associated with malignancy in
patients with dermatomyositis specifically >40 years of age
[1,2]. Thus, even if there is no malignancy at the diagnosis
of dermatomyositis, patients positive for anti-TIF-1γ anti-
bodies should be periodically checked for occurrence of
malignant diseases.

In our case, the tumour size decreased and skin symp-
toms improved after first-line chemotherapy with carbo-
platin and etoposide. Moreover, the levels of anti-TIF-1γ
antibodies after five and seven cycles of amrubicin therapy
were lower and the tumour sizes were smaller than those
at the diagnosis of dermatomyositis. Similar to our results,
Taki et al. reported that the levels of anti-TIF-1γ anti-
bodies decreased with improvement of skin erythema after
chemotherapy in a patient with dermatomyositis and germ
cell tumour [5]. Therefore, the levels of anti-TIF-1γ anti-
bodies could be an indicator of response to chemotherapy
for malignancy. Further studies for longitudinal

evaluations of anti-TIF-1γ antibodies in cancer-associated
dermatomyositis are needed.

Anti-TIF-1γ antibodies carry a relatively low risk for
ILD. Fujimoto et al. reported that four (5.5%) of 73 Japa-
nese patients with anti-TIF-1γ-positive dermatomyositis
had ILD [2]. In another report from a US group, none of
16 anti-TIF-1γ-positive dermatomyositis patients had ILD
[4]. This discrepancy in the prevalence of ILD may be due
to ethnic differences. The interstitial pneumonia of our
patient was mild with normal pulmonary function. Other
connective tissue diseases such as systemic sclerosis and
Sjögren syndrome were not present. Therefore, we con-
consider that her interstitial pneumonia was one of the in-
ternal involvements of cancer-associated dermatomyositis.
Interestingly, primary SCLC and ILD co-existed in the
same lesion (Fig. 2A). Importantly, ILD was not worsened
by cytotoxic chemotherapy without corticosteroid or
immunosuppressant. However, clinical features and patho-
genesis of ILD associated with anti-TIF-1γ antibodies
remain to be elucidated. Future studies are necessary.

Disclosure Statement

Appropriate written informed consent was obtained for
publication of this case report and accompanying images.

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