

## Dermatomyositis Associated with Lung Neuroendocrine Carcinoma

Reina Takashima<sup>1</sup>, Kazufumi Takamatsu<sup>1</sup>, Yutaka Shinkawa<sup>2</sup>, Masato Yagita<sup>2</sup>,  
Motonari Fukui<sup>1</sup> and Masaaki Fujita<sup>2</sup>

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### Abstract

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Dermatomyositis is associated with various types of malignancy. However, the association of dermatomyositis with lung neuroendocrine carcinoma is rare. We herein report a case of dermatomyositis with lung neuroendocrine carcinoma.

**Key words:** dermatomyositis, paraneoplastic syndrome, neuroendocrine carcinoma, lung cancer

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### Introduction

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Dermatomyositis is associated with various types of malignancy (1-5), and the spectrum of associated malignancies parallels that observed in the general population, varying with ethnicity and geographic region. Breast, lung, and colorectal cancers are malignancies commonly associated with dermatomyositis in Western countries (1-4), whereas gastric cancer is the malignancy most commonly associated with dermatomyositis in Japan, followed by colon, ovarian, lung, thymic, and pancreatic cancers (5). The association of nasopharyngeal malignancy with dermatomyositis is also well described in Asian countries (6-9). However, the association of dermatomyositis with lung neuroendocrine carcinoma is rare. We herein report a case of dermatomyositis with lung neuroendocrine carcinoma. In addition, to analyze the published evidence, we conducted a systemic review of the Medline database through PubMed.

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### Case Report

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A 75-year-old man was admitted to Kitano Hospital with muscle weakness, muscle pain, rash, arthralgia, severe dysphagia, and a fever. He had a one-month history of rash on the extensor surfaces of the metacarpophalangeal and interphalangeal joints on both hands and on the eyelids, and a

two-week history of symmetrical proximal muscle weakness in the upper and lower limbs and poor oral intake. He had been smoking 40 cigarettes a day for 40 years. He was a precision polishing worker, with no history of exposure to either radiation or industrial chemicals. A physical examination revealed cutaneous manifestations of Gottron's sign and heliotrope rash. Medical research council (MRC) scale for muscle strength was grade 3 for the upper and lower limb muscles. Laboratory tests showed the following: creatine kinase (CK), 15,242 IU/L (normal, <248 IU/L); myoglobin, 2,504 ng/mL (normal, <73 ng/mL); aldolase, 31.6 U/mL (normal, <4.9 U/ml); C-reactive protein, 2.53 mg/dL (normal, <0.14 mg/dL); and erythrocyte sedimentation rate, 42 mm/h (normal, <20 mm/h). The results for anti-nuclear antibody were positive (1:80, speckled) with the indirect immunofluorescence test (normal, <1:40). Anti-transcriptional intermediary factor 1- $\gamma$  antibody was positive, but negative results were obtained for antibodies to aminoacyl-tRNA synthetases (Jo-1, PL-7, PL-12, OJ, and EJ), signal recognition particle (SRP), melanoma differentiation-associated protein 5 (MDA-5), Ku, and Mi-2. Magnetic resonance imaging showed signal hyperintensities on short T1 inversion recovery images in the deltoid, biceps, triceps, trapezius, infraspinatus, and supraspinatus muscles. Electromyogram and muscle biopsy were not performed. Computed tomography revealed no evidence of interstitial pneumonia. Dermatomyositis was diagnosed based on the criteria of Bohan and Peter

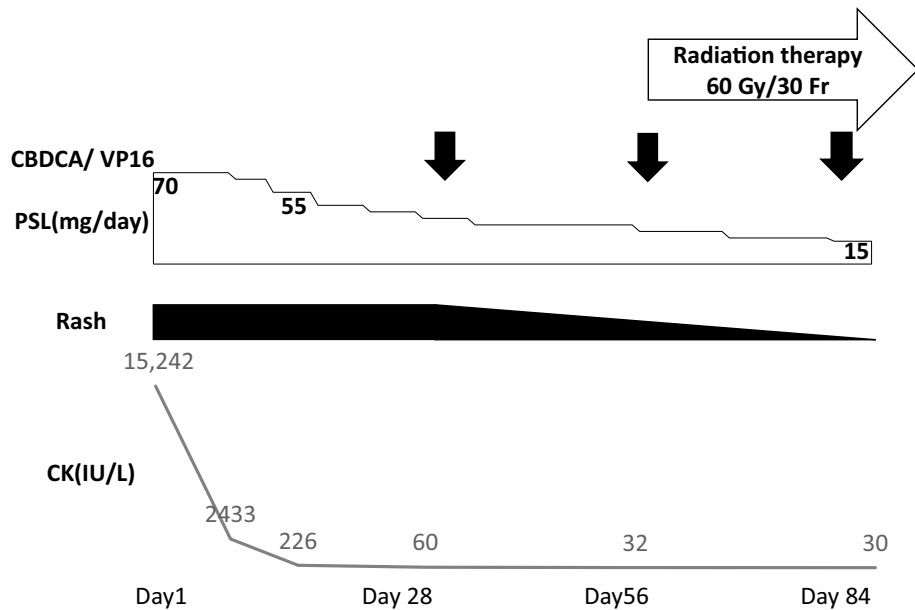
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<sup>1</sup>Respiratory Disease Center, Division of Respiratory Medicine, The Tazuke-Kofukai Medical Research Institute, Kitano Hospital, Japan and

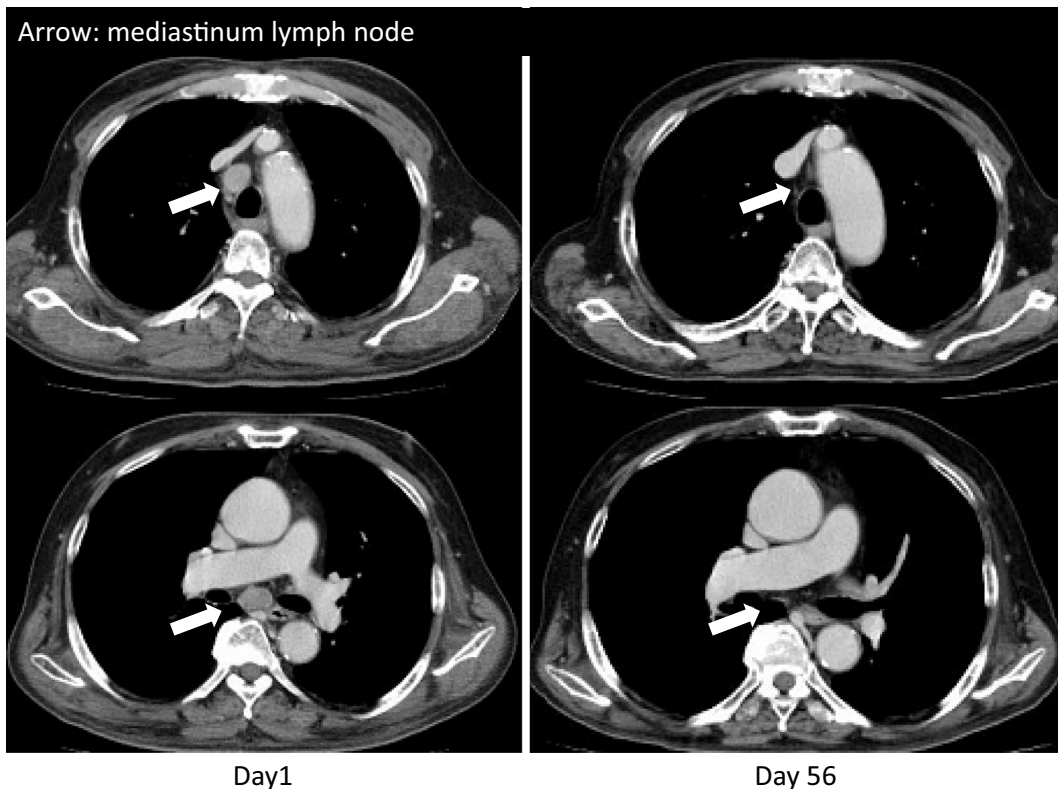
<sup>2</sup>Department of Clinical Immunology and Rheumatology, The Tazuke-Kofukai Medical Research Institute, Kitano Hospital, Japan

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Correspondence to Dr. Masaaki Fujita, ms-fujita@kitano-hp.or.jp



**Figure 1.** The patient's clinical course.

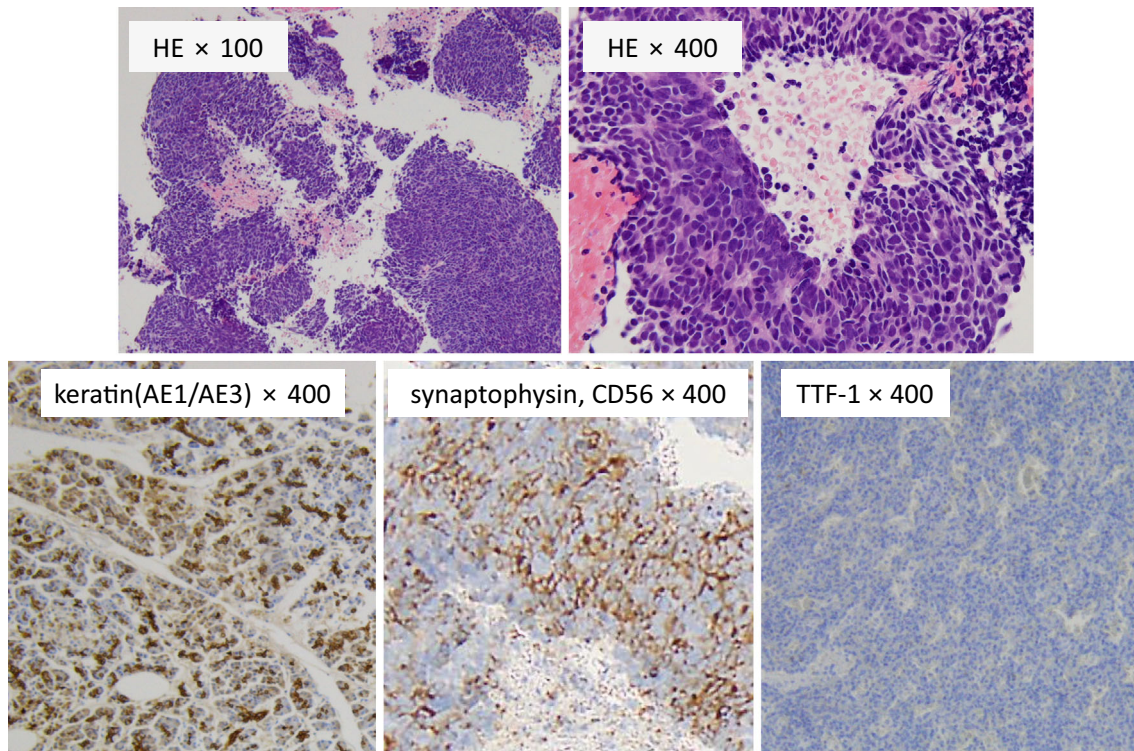


**Figure 2.** Chest computed tomography.

(probable; symmetric proximal muscle weakness, elevation of serum skeletal muscle enzymes, and skin rash) (10, 11). Oral prednisolone (PSL) at 70 mg/day (1 mg/kg/day) was initiated and elicited a prompt response. The patient's clinical course is shown in Fig. 1. The symptoms such as cutaneous manifestations, muscle weakness, and dysphagia, as well as the laboratory data, all promptly improved. The MRC scale for muscle strength became grade 4 for the upper and lower limb muscles. Notably, administration of PSL

improved the patient's oral intake. Muscle enzyme levels normalized (e.g. CK, 226 IU/L; normal, <248 IU/L) by Day 14.

The possibility of malignancy was examined during the diagnosis and treatment of dermatomyositis. Computed tomography revealed a nodule, 13 mm in diameter, in the upper lobe of the right lung and lymph node swelling in the left lower neck and right mediastinum (Fig. 2). No evidence of other primary tumors or metastases was seen in the stom-



**Figure 3.** Histology of a mediastinal lymph node.

ach, colon, liver, kidney, pancreas, prostate, or brain. Furthermore, stomach and colon cancers were not detected on gastroscopy and colonoscopy. Analyses of tumor markers showed the following: carcinoembryonic antigen, 1.2 ng/mL (normal, <5 ng/mL); carbohydrate antigen 19-9, 2.2 U/mL (normal, <37 U/mL); cytokeratin 19 fragment, 1.82 ng/mL (normal, <2.08 ng/mL); squamous cell carcinoma antigen, 0.6 ng/mL (normal, <2.0 ng/mL); neuron specific  $\gamma$ -enolase, 83.7 ng/mL (normal, <16.3 ng/mL); and pro-gastrin-releasing peptide, 24.1 pg/mL (normal, <81 pg/mL). Biopsy of a mediastinal lymph node was performed by endoscopic ultrasound-guided fine needle aspiration (Fig. 3). The tumor cells were of a medium size and had a high nuclear-cytoplasmic ratio, fine chromatin, and inconspicuous nucleoli. Immunohistochemically, the tumor cells were positive for cytokeratin (AE1/AE3), partially positive for synaptophysin and CD56, and negative for thyroid transcription factor 1. Based on these findings, lung neuroendocrine carcinoma (large cell neuroendocrine carcinoma [LCNEC] or small cell lung cancer [SCLC]; TxN3M0) was diagnosed. A cytological diagnosis of LCNEC or SCLC could not be made in our case, as SCLC is difficult to distinguish from LCNEC in some cases (12, 13). The final diagnosis was lung neuroendocrine carcinoma associated with dermatomyositis.

On Day 15, the dose of PSL was decreased to 55 mg/day, and chemotherapy with carboplatin and etoposide was initiated. Chemotherapy was repeated monthly. The patient received four cycles of chemotherapy. Whether patients diagnosed with lung neuroendocrine carcinoma should be treated with non-SCLC (NSCLC)- or SCLC-based regimens remains

unclear (14-16). Current treatment strategies for patients with lung neuroendocrine carcinoma are a mixture between the guidelines for NSCLC and SCLC patients (17). As we were unable to distinguish SCLC from LCNEC in our case, the patient was treated in accordance with the standard international protocol for SCLC (17, 18).

Within two weeks after starting chemotherapy, his muscle power had normalized, and the CK level had decreased to 54 IU/L. The MRC scale for muscle strength became grade 5 for the upper and lower limb muscles. The cutaneous manifestations were improved two months after starting chemotherapy. The swelling in the mediastinum lymph nodes also disappeared two months after starting chemotherapy (Fig. 2). PSL was successfully tapered to 15 mg/day after 3 months and 10 mg/day after 6 months. No complications associated with immunosuppression were identified during the clinical course. As of the time of writing, 5 months after completion of chemotherapy, the patient is continuing to receive 7 mg/day of PSL.

### Systemic review

We conducted a systemic review of the Medline database through the PubMed website of articles published from January 1947 to December 2015 using a combination of the following terms: “dermatomyositis”, “small cell lung”, and “lung neuroendocrine”. Non-English articles were excluded. We identified a total of 60 English full-text articles using these search terms, including 16 cases of dermatomyositis associated with lung neuroendocrine tumor (large cell neuroendocrine carcinoma or small cell lung cancer).

**Table. Dermatomyositis Associated with Lung Neuroendocrine Carcinoma.**

Reference	Age / Sex	Diagnosis	Initial treatments	Response: cutaneous manifestations	Response: muscular manifestations	Final outcome
20	55/M	SCLC	None	N.S.	N.S.	Dead
21	44/M	SCLC	PSL (60 mg), chemotherapy	Gradual improvement	Gradual improvement	Dead
22	47/M	SCLC	N.S.	N.S.	N.S.	N.S
23	67/M	SCLC	Chemotherapy	Dramatic improvement	Dramatic improvement	N.S
24	58/F	SCLC	PSL, azathioprine	Dramatic improvement	Dramatic improvement	N.S
25	68/F	SCLC	PSL, chemotherapy, radiotherapy	N.S.	N.S.	Dead
26	65/M	SCLC	Chemotherapy	N.S.	No improvement	Dead
27	55/F	SCLC	Surgery, chemotherapy radiotherapy	Improvement	Improvement	Alive
28	74/F	SCLC	Radiotherapy, chemotherapy	N.S.	N.S.	Dead
29	60/M	SCLC	PSL, chemotherapy, radiotherapy	Significant improvement	Significant improvement	Dead
30	57/M	SCLC	IVIg	Rapid improvement	No improvement	Dead
31	79/M	SCLC	PSL, IVIg	Improvement	Improvement	Dead
32	62/M	SCLC	Steroid	Relieved	N.S.	N.S
33	52/F	SCLC	PSL→chemotherapy	N.S.	Rapid improvement	Alive
34	52/M	SCLC or LCNEC	PSL→chemotherapy	Gradual improvement	Gradual improvement	Dead
35	62/M	SCLC	PSL→chemotherapy	Marked improvement	Marked improvement	Alive
Our case	75/M	SCLC or LCNEC	PSL→chemotherapy	Gradual improvement	Rapid improvement	Alive

M: male, F: female, SCLC: small cell lung cancer, PSL: prednisolone, N.S.: Not specified, LCNEC: large cell neuroendocrine carcinoma, IVIg: intravenous, immunoglobulin

## Discussion

Dermatomyositis is associated with various types of malignancy. However, the association of dermatomyositis with lung neuroendocrine carcinoma is rare. We herein report a case of dermatomyositis with lung neuroendocrine carcinoma. Dermatomyositis associated with malignancy is generally more resistant to corticosteroids than idiopathic dermatomyositis (19). In some cases, removal of the coexisting malignancy reportedly improves dermatomyositis and/or achieves good response to corticosteroids (19). However, whether the association of dermatomyositis with lung neuroendocrine carcinoma results in resistance to corticosteroids is still unclear. To analyze the published evidence, we

conducted a systemic review, identifying 16 cases of dermatomyositis associated with lung neuroendocrine tumor (SCLC or LCNEC) reported as English full-text articles (Table) (20-35). Seven cases had been treated with chemotherapy, radiotherapy, and/or surgery for an existing tumor (21, 23, 25-29). Another four cases had been treated with corticosteroids alone or corticosteroids prior to chemotherapy (32-35), one case with corticosteroids and azathioprine (24), one case with intravenous immunoglobulin (IVIg) alone (30), and one case with corticosteroids and IVIg (31). No information about treatment was available for the remaining two reports.

In most cases, the symptoms of dermatomyositis improved even though the final prognosis was poor due to the underlying malignancy. Interestingly, both Labinjoh et al.

and Albert et al. reported cases of dermatomyositis with SCLC that showed a prompt response to corticosteroids before chemotherapy (33, 35). Chao et al. reported a case of dermatomyositis with SCLC that showed a response to corticosteroids without chemotherapy (32). Murakami et al. reported a case of dermatomyositis with lung neuroendocrine carcinoma (SCLC or LCNEC) that showed a gradual response to corticosteroids before chemotherapy (34). Antonioli et al. reported a case of dermatomyositis with SCLC that showed a response to the combination of corticosteroids and IVIg (31). In our case, the patient's muscle weakness and dysphagia improved with corticosteroid therapy before chemotherapy, although the cutaneous and muscular manifestations were further improved after chemotherapy. Notably, administration of PSL improved the patient's oral intake and normalized the CK levels before the start of chemotherapy.

Given these present findings, while the efficacy of corticosteroids alone in treating dermatomyositis associated with lung neuroendocrine tumor is yet to be confirmed, corticosteroids prior to chemotherapy may be an option for improving the performance status of a patient, even if the patient has little chance of curing the associated cancer.

All of the procedures performed in the studies involving human participants were conducted in accordance with the ethical standards of the institutional committee and with the 1964 Declaration of Helsinki and its later amendments.

Informed consent was obtained from the participant described in the study.

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

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