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【 CASE REPORT 】

Advanced Lung Adenocarcinoma with Nivolumab-associated Dermatomyositis

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Abstract:
We herein report a 42-year-old man with advanced lung adenocarcinoma and nivolumab-associated dermatomyositis. Nivolumab, an anticancer drug that is classified as an immune checkpoint inhibitor, often induces immune-related adverse events (irAEs). However, there have so far been no reports regarding nivolumab-associated dermatomyositis. This patient was diagnosed with dermatomyositis due to the presence of proximal muscle weakness with abnormal electromyography and magnetic resonance imaging findings; skin lesions, such as heliotrope rash, shawl sign, and periungual erythema; and an elevated serum aldolase level after nivolumab administration. It is important to consider drug-associated dermatomyositis in the differential diagnosis of patients presenting with skin lesions and muscle weakness after nivolumab treatment.

Key words: nivolumab, dermatomyositis, lung cancer, immune-related adverse event

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Introduction

Nivolumab is a human IgG4 monoclonal antibody that targets the programmed cell death 1 (PD-1) receptor and is classified as an immune checkpoint inhibitor. Borghaei et al. recently reported the results of a phase III study (Checkmate 057 clinical trial), in which nivolumab (3 mg/kg every 2 weeks) or docetaxel (75 mg/m^2 every 3 weeks) was administered to patients with advanced nonsquamous non-small-cell lung cancer, who had previously received platinum-based chemotherapy. The results of this study demonstrated that overall survival was longer for patients who received nivolumab than for those who received docetaxel (1). Therefore, nivolumab treatment has become a standard treatment for patients with lung cancer, and the frequency of administering nivolumab treatments is therefore rapidly increasing. However, this drug has the potential to cause immune-related adverse events (irAEs), such as skin, gastrointestinal, hepatic, and endocrine pathologies. To our knowledge, this is the first report of a patient with lung adenocarcinoma who was treated with nivolumab and whose condition fulfilled all the diagnostic criteria for dermatomyositis as an irAE (2).

Case Report

A 42-year-old male, who had a history of smoking one cigarette pack per day for 20 years, was diagnosed with right lung adenocarcinoma with malignant pleural effusion (cT2aN0M1a stage IV) 2 years and 3 months before starting nivolumab therapy. No *EGFR* mutations and the *ALK* fusion oncogene were detected in this patient, who received first-line chemotherapy that consisted of 4 cycles of cisplatin, pemetrexed, and bevacizumab followed by 7 cycles of maintenance therapy with pemetrexed and bevacizumab, and 4 cy-

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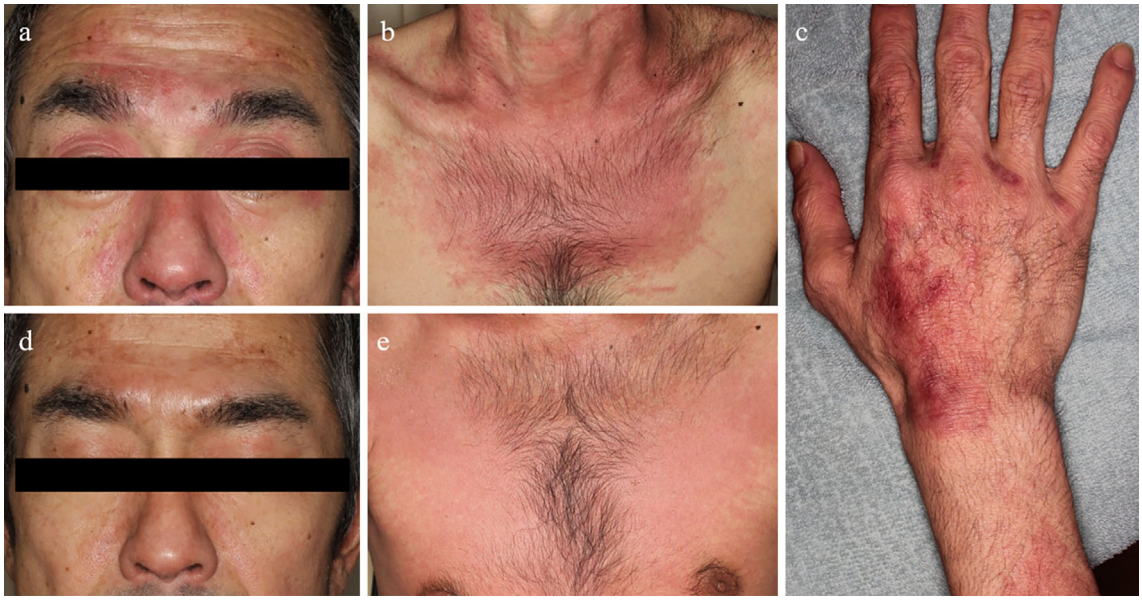

Figure 1. **Dermatological findings at 1.5 months after nivolumab treatment show heliotrope eruption (a), shawl sign (b), and periungual erythema (c). Dermatological findings before steroid therapy at 1 month after nivolumab discontinuation show partial scabbing with an improvement of the symptoms (d, e).**

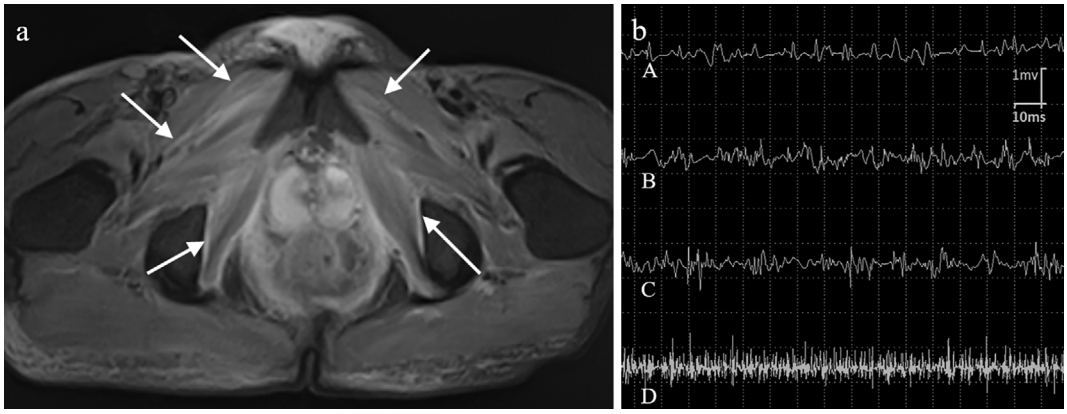

Figure 2. **a: Magnetic resonance imaging of skeletal muscles reveal abnormal hyper intensity areas (arrows), b: Electromyography of biceps brachii (A), deltoid (B), and external carpi radialis (C, D), all of which display low amplitudes.**

cles of docetaxel as second-line chemotherapy. Upon treatment completion, liver and adrenal metastases, in addition to cervical, axillary, mediastinum, and para-aortic lymph node metastases, were detected, and nivolumab (3 mg/kg, biweekly) was initiated as third-line chemotherapy.

The patient experienced general fatigue and minor proximal limb muscle weakness, without demonstrating any abnormal laboratory data or physical symptoms upon examination, a few days after initial nivolumab administration. Grade 1 skin redness, according to Common Terminology Criteria for Adverse Events, appeared on the patient's left lower leg one week after administration. Nivolumab treatment was therefore discontinued after a total of three courses over one month, due to the appearance of clear proximal muscle weakness six weeks after the initial administration. The patient presented with skin lesions that increased in size and spread all over his face, left ears, back, and hip within two months of the initial administration, and he also demonstrated heliotrope rash, shawl sign, and periungual erythema, which are consistent with the symptoms of cutaneous dermatomyositis (Fig. 1a-c). After ceasing nivolumab treatment, the skin lesions partially and gradually resolved. Magnetic resonance imaging (MRI) of the patient's legs revealed abnormally high intensity areas in the bilateral adductor and obturator muscles during short tau inversion recovery images (Fig. 2a), and an electromyogram revealed typical myogenic conversion (Fig. 2b). On the other hand, the patient's muscle weakness worsened to the point that squatting was not possible, and the patient was hospitalized for 3 months after the initial nivolumab administration.

Physical examination of the patient upon admission revealed cervical and axillar lymph node enlargement, and

Table. Laboratory Data at the Time of Diagnosis of Dermatomyositis.

CBC		Serology	
WBC	11,960 /μL	CRP	0.65 mg/dL
Neu	74 %	RF	10 IU/L
Lym	10 %	ANA	1:80
Mono	6 %	Anti-ARS-Ab	(-)
RBC	426×10⁴ /μL	Anti-Jo1-Ab	(-)
Hb	13.2 g/dL	Anti-RNP-Ab	(-)
Ht	40.3 %	Anti-SSA-Ab	(-)
Plt	51.2×10⁴ /μL	Anti-SSB-Ab	(-)
Chemistry		KL-6	256 U/mL
HbA1c	6.0 %	TSH	4.772 μIU/mL
TP	5.4 g/dL	F-T3	1.03 μg/dL
Alb	2.2 g/dL	F-T4	2.39 μg/dL
T.Bil	0.50 mg/dL	Tumor marker	
AST	40 IU/L	CEA	308.1 ng/mL
ALT	34 IU/L	SLX	320 U/mL
LDH	738 IU/L		
CK	63 IU/L		
Aldolase	23.7 IU/L		
ALP	255 mU/mL		
BUN	16 mg/dL		
Cre	0.68 mg/dL		
Na	136 mEq/L		
K	5.3 mEq/L		
Cl	101 mEq/L		

skin lesions with partial scabbing (Fig. 1d and e). The patient's muscle strength was slightly weakened at grade 4, according to the score of Manual Muscle Testing (MMT) of the biceps, triceps, iliopsoas, quadriceps, hamstrings, anterior tibialis, and gastrocnemius without laterality, and the patient also complained of muscle pain when grasping with his limbs. Laboratory data (Table) revealed creatine kinase (CK) levels of 137 mU/mL, while WBC was 11,960 μL, C-reactive protein (CRP) 0.65 mg/dL, and aldolase elevated to 23.7 IU. Anti-Jo-1 and anti-aminoacyl-tRNA synthetase (ARS) antibodies were negative. A chest X-ray scan showed right pleural effusion, and a chest and abdominal computed tomography (CT) scan showed right pleural effusion, multiple mediastinal and hilar lymph node swelling, and multiple adrenal and liver metastases.

The condition of the patient fulfilled definite diagnostic criteria for dermatomyositis, based on the Bohan and Peter criteria, and the presence of typical skin lesions, proximal muscle weakness in extremities, elevated serum aldolase levels, muscle pain upon grasping, and abnormal MRI and electromyogram results (2). After admission, we began to administer prednisolone (0.6 mg/kg daily) treatment and the patient's symptoms slightly and temporarily improved. However, progressive muscle weakness, new back pain, and lower leg numbness were encountered one week after steroid therapy, and a urination disorder appeared two weeks after steroid therapy. We suspected the presence of a spinal cord disorder, based on the neurological findings, including

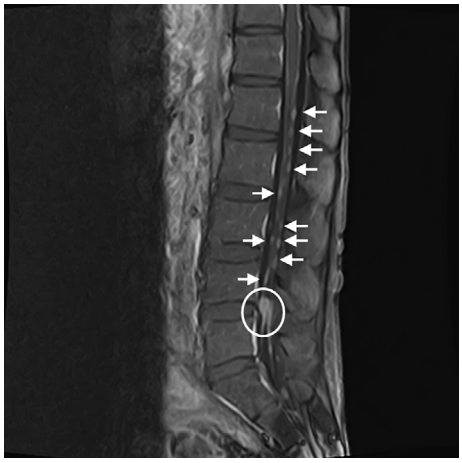

Figure 3. Vertebral magnetic resonance imaging shows multiple spinal cord and meningeal dissemination (arrows and circle).

newly occurring leg paralysis, and general sensory disorder. A spinal MRI of the patient revealed an abnormally high intensity lesion in the C5/6 level cervical cord, with abnormal contrast, and a tumor with abnormal contrast on the left side of the L4/5 level vertebral canal (Fig. 3). The patient was diagnosed with multiple spinal cord and meningeal disseminations ten days after steroid therapy and died due to lung cancer progression five months after the start of nivolumab treatment.

Discussion

We report a patient with advanced lung adenocarcinoma who developed dermatomyositis as an irAE after nivolumab treatment.

It has been reported that Pthe D-1 inhibitor-related dermatologic characteristics consist of erymatous mascules, papules, and plaques that predominantly localize to the trunk and extremities (3). In this case, the initial eruption presented only as lower leg erythema, but progressive dermatologic findings revealed skin lesions typical of dermatomyositis. To our knowledge, this is the first report discussing nivolumab-associated dermatomyositis though there is a case report of a patient with melanoma who presented with drug-associated dermatomyositis as an irAE after ipilimumab treatment which targets a cytotoxic T-lymphocyte antigen (4).

Dermatomyositis is an idiopathic inflammatory myopathy that presents as proximal skeletal muscle weakness, muscle inflammation, and a variety of skin manifestations. While the etiology of this disease remains unknown, the mechanisms of dermatomyositis are suggested to evoke type 1 interferon interactions associated with CD4+ cells, in several different models (5). Conversely, nivolumab is a human IgG 4 PD-1 immune-checkpoint-inhibitor antibody, and in cancer cells that express PD-1 ligands, PD-L1 and PD-L2, ligand binding to PD-1 results in the downregulation of human T-

cell activation and it also promotes tumor immune escape. Nivolumab blocks PD-1-mediated signaling and restores antitumor immunity, however, this drug may trigger dermatomyositis as one type of irAE due to compromised immunosuppression, through an excessive immune reaction derived from T cell activation and following an increase in the production of interferonγ (1, 6, 7).

In this report, the patient's lung cancer became progressive after nivolumab treatment. It has been reported that dermatomyositis complicates cancer in 9-30 % of patients, as a paraneoplastic syndrome (8, 9). Regarding the pathogenesis, it is considered that the antigens that target an immune response are important for evoking a paraneoplastic disorder (10). The skin lesions observed in this case appeared after nivolumab treatment and showed improvement and resolution before steroid therapy, after discontinuing nivolumab, as shown in Fig. 1. Regarding the progressive muscle weakness seen in this case, we hypothesize that the proximal muscle weakness observed in the early phases was myositis-specific, because of MRI and electromyogram abnormalities, while muscle weakness in later phases may have been associated with leg paralysis due to meningeal disseminations. Therefore, we suspect that the occurrence of dermatomyositis in this case was due to nivolumab treatment, rather than a paraneoplastic disorder that accompanied cancer progression. However, this occurrence might have been enhanced by cancer progression in combination with a nivolumab-induced immune reaction, and it has been reported that patients with cancer treated with anti-PD-1 monotherapy occasionally experience hyperprogressive disease such as that observed in this case (11). Recently, several studies have found that cancer-associated myositis in adults is associated with antibodies against transcription intermediary factor-1 gamma and nuclear matrix protein-2, although we did not investigate these antibodies in this case (12). Additional investigations into how dermatomyositis develops in a nivolumab treatment setting are required.

The use of prednisolone is the standard treatment for dermatomyositis, including irAEs incidences (4, 13). However, aggressive treatments, including surgery and/or chemotherapy, for cancer may be the optimal choice for the treatment of cancer-related dermatomyositis, such as paraneoplastic disorder (14). In this case, chemotherapy was not chosen due to the patient's poor cancer response rate and performance status.

Aldolase concentrations are occasionally elevated in patients with myositis who have normal CK levels, such as in this case, and CK is the most widely used enzyme to diagnose and follow muscle diseases (15). We hypothesize that aldolase measurements could allow for an earlier diagnosis of myositis.

The overall health status results of Checkmate 057 indicate that patients who underwent nivolumab treatment displayed significantly improved symptoms and better qualities of life after treatment (16). Therefore, it is important to consider primary disease progression in the presence of irAEs and perform detailed medical examinations when rare symptoms, such as those pertaining to this case, develop.

Conclusion

We herein reported the first known case of nivolumab-associated dermatomyositis in a patient with lung cancer. It is necessary to consider the progression of the cancer in addition to irAEs when using immune-checkpoint inhibitors, such as nivolumab. We suspect that the frequency of irAEs may increase as the use of immune-checkpoint inhibitors increases for various types of cancer. Therefore, it is crucial to maintain close and constant detailed communication between the treating oncologist and general physician.

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

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