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【 CASE REPORT 】

Atezolizumab-associated Dermatomyositis in Advanced Small-cell Lung Carcinoma

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Abstract:
Dermatomyositis is a rare immune-related adverse event caused by immune checkpoint inhibitors. We herein report a 75-year-old Japanese man with small-cell lung carcinoma who developed dermatomyositis after the administration of atezolizumab. He developed rashes on day 13 and myalgia and motor weakness on day 30 of the first administration of atezolizumab. Anti-transcriptional intermediary factor 1-gamma antibody was positive, and serum interleukin-6 levels were prominently elevated in the acute phase. Symptoms were improved by corticosteroid therapy. This is the first report of dermatomyositis associated with atezolizumab. Clinicians should be aware of the possibility of dermatomyositis after the administration of immune checkpoint inhibitors.

Key words: anti-transcriptional intermediary factor 1-gammma antibody, atezolizumab, dermatomyositis, immune checkpoint inhibitor, immune-related adverse event, interleukin-6

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Introduction

Immune checkpoint inhibitors (ICIs) that target programmed death 1, programmed death ligand 1 or cytotoxic T lymphocyte-associated protein 4 (CTLA4) have shown efficacy and safety in the treatment of various advanced malignant disease. Atezolizumab, an ICI targeting programmed death ligand 1, has been approved for the treatment of advanced urothelial carcinoma, non-small- or small-cell lung cancer, triple-negative breast cancer, hepatocellular carcinoma, and melanoma by the Food and Drug Administration in the United States (1).

ICIs can induce autoimmune side effects called immune-related adverse events (irAEs) due to an exaggerated inflammatory response (2, 3). These irAEs can affect various organs, most commonly the skin, liver, gastrointestinal tract, and endocrine glands, but less often the lungs, kidneys, heart, hematologic system, peripheral or central nervous systems, and skeletal muscle (2, 3). Although ICIs are widely used in the clinical treatment of patients with advanced malignant diseases, the management of rare irAEs, including the diagnosis and treatment, is not well established. Clinicians thus have to deal with rare manifestations of irAEs on a case-by-case basis.

Dermatomyositis is a rare irAE, and to our knowledge, only four cases have been reported (4-7). Furthermore, dermatomyositis associated with atezolizumab has not been reported previously. Because dermatomyositis is often associated with malignancy, discriminating between ICI-associated dermatomyositis and cancer-associated dermatomyositis can be challenging (8).

We herein report a case of dermatomyositis associated with atezolizumab treatment.

Case Report

A 75-year-old Japanese man was diagnosed with small-cell lung carcinoma by endobronchial ultrasound-guided transbronchial needle aspiration of a right lung tumor. Positron emission tomography and computed tomography revealed metastatic lesions in the right adrenal gland and rib bones, suggesting advanced-stage carcinoma (cT2aN3M1b, stage IVB). He was initially treated with atezolizumab, car-

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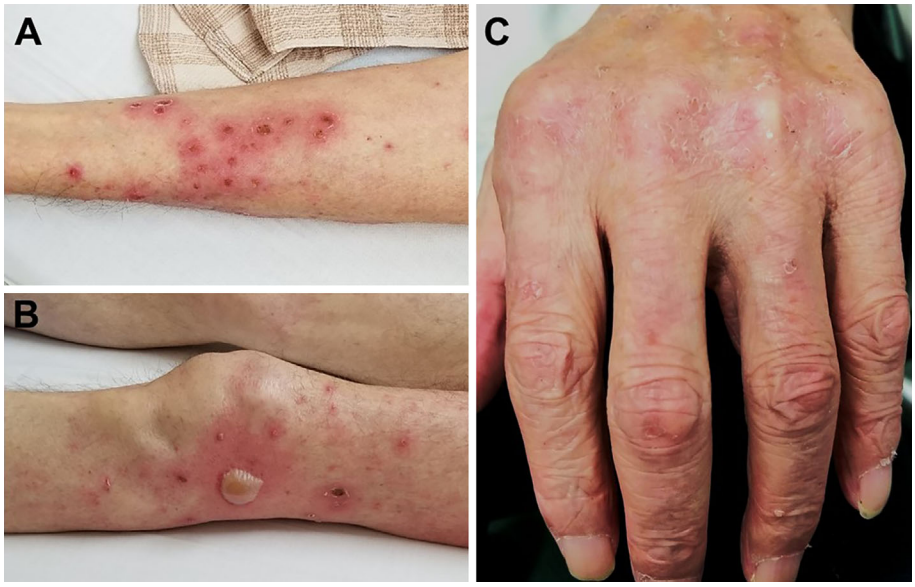

Figure 1. Eruptions on the patient on admission. Erythemas with eschars or bullae are seen on the forearm (A) and leg (B). Violaceous erythematous eruptions are present over the extensor surfaces of the metacarpophalangeal joints and proximal interphalangeal joints of the hands (Gottron's sign) (C).

boplatin, and etoposide. The level of creatine kinase (CK) before administration of atezolizumab was 70 U/L (normal, 54-248 U/L). On day 13 of treatment, the patient developed rashes in the upper limbs and trunk. As irAEs of the skin (Grade 2) were suspected, atezolizumab was discontinued, and he received a second course of chemotherapy with carboplatin plus etoposide on day 21. The rashes expanded to the lower limbs, and he subsequently presented with myalgia and weakness in the proximal limbs on day 30.

The patient was admitted on day 35, presenting with muscle grasp pain and motor weakness in the proximal extremities (manual muscle test, 4). He was afebrile, showing no ptosis, diplopia, dysarthria, dysphagia, ataxia, or sensory disturbance. He presented with erythema and eschars or bullae in the bilateral forearms and legs (Fig. 1A, B). Although "heliotrope rash" and "V sign rash" as characteristic skin findings in dermatomyositis were not recognized, the patient presented with violaceous erythematous eruption over the extensor surfaces of the metacarpophalangeal joints and proximal interphalangeal joints of his hands, suggesting "Gottron's sign" (Fig. 1C). Blood testing revealed that CK, myoglobin, and aldolase were markedly elevated, at 5,698 U/L, 1,257 μg/mL (normal, <97 μg/mL), and 51.5 U/L (normal, 2.1-6.1 U/L), respectively. The concentration of C-reactive protein was slightly increased to 3.341 mg/dL (normal, <0.3 mg/dL). Myositis-specific autoantibodies including anti-Jo-1 and anti-signal recognition particle antibodies were negative. However, the index of anti-transcriptional intermediary factor 1-gamma (TIF1-γ) antibody (9, 10) was elevated to 75 (normal, <32).

Needle electromyography in the right vastus medialis muscle showed normal interference patterns at low voltage, suggesting myogenic changes. Magnetic resonance imaging of the muscle showed heterogeneous hyperintensities in bilateral thigh muscles on short-T1 inversion recovery imaging, indicating the presence of myositis (Fig. 2). Serum interleukin (IL)-6 was markedly elevated at 32.2 pg/mL (normal, <4.0 pg/mL).

Because the patient met Bohan and Peter's diagnostic criteria for dermatomyositis (definite case) (11) and the symptoms had been recognized only after initiating atezolizumab administration, we diagnosed him with dermatomyositis induced by atezolizumab. A skin biopsy of the erythema on the right thigh showed histopathological findings of vacuolar interface dermatitis, consistent with the histopathological findings of both drug eruption and dermatomyositis (Fig. 3). The patient declined to a undergo muscle biopsy because of the invasiveness.

Intravenous prednisolone was initiated at 45 mg/day (1 mg/kg/day) on day 37. Because CK was elevated to 8,014 U/L on admission day 3, steroid pulse therapy with methylprednisolone was started at 1,000 mg/day for 3 days. After this steroid pulse therapy, oral administration of prednisolone was started at 45 mg/day (0.5 mg/kg/day) and tapered.

Eruptions, muscle weakness, and muscle grasp pain gradually improved. The CK levels decreased markedly. Because delirium developed, possibly induced by prednisolone, he was discharged on day 53 and continued to be monitored as an outpatient. CK and muscle weakness were normalized on day 60. The oral administration of prednisolone was finished on day 78. However, erythema in the extremities was exacerbated on day 83. He resumed oral prednisolone at 25 mg/day on day 89, and the erythema improved. After tapering the dose of prednisolone, a maintenance dose of 5 mg/day was continued. The IL-6 level normalized to 2.0 pg/ml (normal, <4.0 pg/mL) on day 122. Thereafter, no relapse of

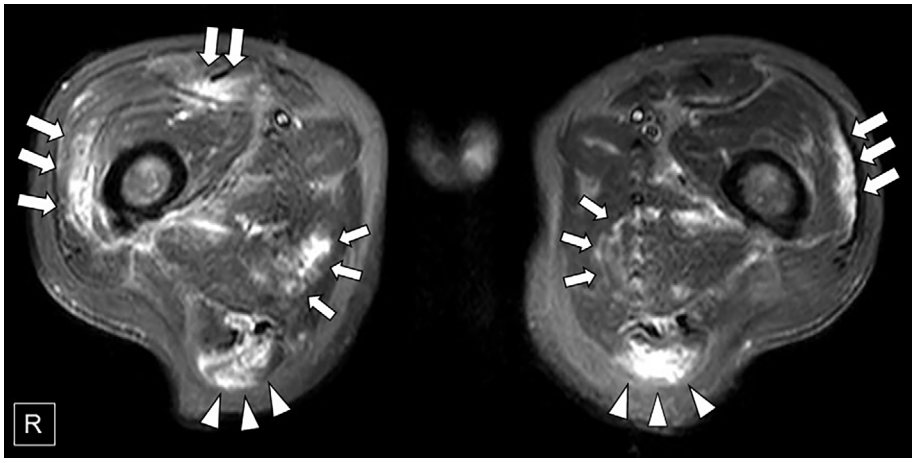

Figure 2. **Myositis demonstrated by magnetic resonance imaging of the thigh muscles. Heterogeneous hyperintensities are evident in bilateral quadriceps femoris muscles (large arrows), adductor magnus muscles (small arrows), and hamstrings (arrowheads) on short-T1 inversion recovery images.**

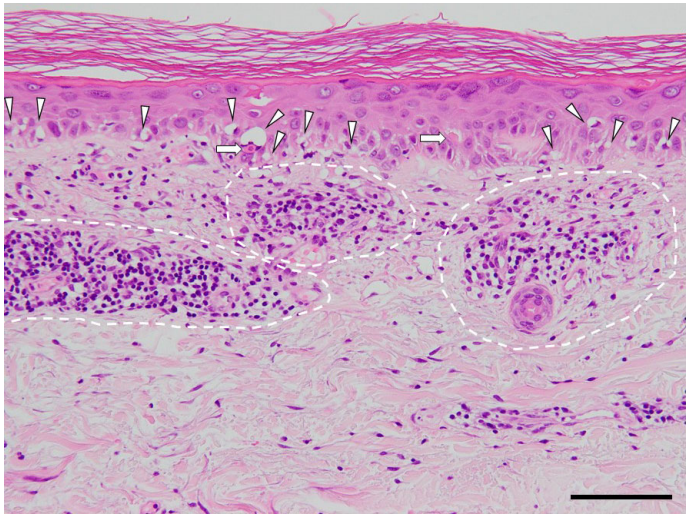

Figure 3. **Histopathology of a skin biopsy of the erythema of the right thigh (Hematoxylin and Eosin staining). Vacuolization (arrowheads) and necrotic keratinocytes (arrows) are found at the dermoepidermal junction. Edema and perivascular lymphocytic infiltrates (dashed circles) are found in the upper dermis. These histopathological findings suggest vacuolar interface dermatitis, consistent with the histopathologies of both drug eruption and dermatomyositis. Scale bar=100 μm.**

dermatomyositis symptoms was identified.

Discussion

A case of dermatomyositis associated with atezolizumab was presented. Dermatomyositis has rarely been reported as an irAE, with only four such cases found in the literature (4-7). The present description represents the fifth report of dermatomyositis associated with ICI treatment. The OAK study (12) and IMpower150 Study (13), as randomized phase 3 trials of atezolizumab therapy, found no cases of irAEs presenting as dermatomyositis. This is the first report of dermatomyositis associated with atezolizumab. Furthermore, this is the first description of dermatomyositis due to ICI in which the serum level of IL-6 was measured.

Characteristics of cases of dermatomyositis due to ICIs have also been reported (Table). Two cases developed dermatomyositis following ipilimumab administration (4, 5), and two developed dermatomyositis following nivolumab administration (6, 7). All four cases developed dermatomyositis after one or three doses of each ICI. In three cases (4, 5, 7), dermatitis preceded myositis, as in our case. In the remaining case, dermatitis and myositis occurred simultaneously. Myositis-specific antibodies were detected in two cases: one with anti-TIF-γ antibody (5) and one with anti-aminoacyl tRNA synthetase antibody (7). The levels of serum cytokines, including IL-6, were not measured in those four cases. A skin biopsy was performed in one case, and a pathological examination showed edema and mucin deposition in the upper dermis and lymphocytic infiltrates (5). A

Table. Clinical Characteristics of Cases of Dermatomyositis Due to Immune Checkpoint Inhibitors.

Ref.	Age Sex	ICI	Cancer	Timing of onset		Antibodies	Muscle MRI	Histology	Treatment	Outcome
				Dermatitis	Myositis					
4	50s F	Ip	MM	after first dose	after third dose	ANA 640x	hyper-intensities on STIR	(Muscle) no evidence of inflammatory myositis	PSL	improved
5	70 M	Ip	LSCC	after third dose	two months after onset of dermatitis	ANA 640x anti-TIF1-γ	N.E.	(Skin) edema and mucin deposition in upper dermis and lymphocytic infiltrates	PSL IVIg	improved
6	42 M	Ni	LAC	after first dose	after third dose	none	hyper-intensities on STIR	N.E.	PSL	improved
7	85 F	Ni	MM	after third dose	after third dose	ANA 80x anti-ARS	N.E.	N.E.	PSL	improved
Present case	78 M	At	LSCC	after first dose	after first dose	anti-TIF1-γ	hyper-intensities on STIR	(Skin) vacuolar interface dermatitis	mPSL PSL	improved

ANA: antinuclear antibody, ARS: aminoacyl-tRNA synthetase, At: atezolizumab, ICI: immune checkpoint inhibitor, Ip: ipilimumab, IVIg: intravenous immunoglobulin, LAC: lung adenocarcinoma, LSCC: lung small cell carcinoma, MM: malignant melanoma, mPSL: methylprednisolone, MRI: magnetic resonance imaging, N.E.: not examined, Ni: nivolumab, PSL: prednisolone, Ref.: reference, STIR: short TI inversion recovery, TIF1-γ: transcriptional intermediary factor 1-gamma

muscle biopsy was performed in one case, showing no evidence of inflammatory myositis on a pathological examination, although the biopsy was performed over six days after initiating systemic corticosteroids (4). Because few cases are available for a pathological examination, further histological investigations, including immunostaining, are needed to clarify whether or not dermatomyositis due to irAE exhibits specific pathological findings.

As in our case, abnormal intensities on muscle MRI were observed in two cases (4, 6), suggesting the utility of muscle MRI for demonstrating the presence of myositis due to irAEs. Although the management of dermatomyositis due to irAEs has not been well-established, high-dose corticosteroid is recommended as an initial treatment (14). All 4 cases were treated with prednisolone (50-60 mg or 0.5-0.6 mg/kg), and responses to steroid therapy were generally favorable, although two cases died due to cancer progression (5, 6). Intravenous immunoglobulin was added in one case due to the onset of myositis under corticosteroid administration for dermatitis (5). How long corticosteroids should be continued and how rapidly the doses can be tapered remain unclear.

The distinctive features of the present case were positivity for anti-TIF1-γ antibody and elevated serum IL-6 levels in the acute phase. Because anti-TIF1-γ antibody has been associated with paraneoplastic dermatomyositis (9, 10), whether the present case involved dermatomyositis as an irAE of atezolizumab or was associated with cancer merits further discussion. We diagnosed our case as dermatomyositis due to an irAE of atezolizumab for two main reasons. One was the timing of the onset of dermatomyositis in our case. If any symptoms of dermatitis or myositis had preceded ICI administration, the diagnosis would have been paraneoplastic dermatomyositis (8). However, in the present case, symptoms of both dermatitis and myositis occurred after the dose of atezolizumab. This time course supports the possibility of an irAE of atezolizumab. The other point was the elevated serum level of IL-6. As a pleiotropic cytokine, IL-6 is associated with a wide range of biological activities in immune regulation, hematopoiesis, inflammation, and oncogenesis (15). ICIs can provoke a cytokine-associated toxic status, also known as cytokine release syndrome (CRS). Among a variety of cytokines, IL-6 plays a central role in CRS (16). A previous study demonstrated that patients with nivolumab-associated psoriasiform dermatitis or with other irAEs exhibited increased serum IL-6 levels after treatment with nivolumab, an ICI targeting programmed death 1, while the serum levels of IL-6 were decreased in patients without any irAEs after nivolumab treatment (17). In addition, one report described a patient with metastatic lung adenocarcinoma who developed immune pneumonitis as an irAE with elevated IL-6 levels (18). Similarly, another case report described a sarcoma patient who developed CRS after nivolumab treatment with a high level of IL-6 (19). Interestingly, these two cases were treated with corticosteroids and tocilizumab, an anti-IL-6 receptor monoclonal antibody, and the symptoms were significantly improved after tocilizumab administration. These findings suggest the possibility of IL-6 as a potential biomarker for irAEs (17, 18). Because we did not examine anti-TIF1-γ antibody in the serum before atezolizumab treatment in our case, whether or not the antibody was induced by atezolizumab remains unclear. We therefore cannot rule out the possibility that the present patient had a pre-existing subclinical autoimmune status susceptible to the development of dermatomyositis, with the onset evoked by the administration of atezolizumab, as sug-

gested in previous reports (8, 20). However, we feel that the time course of the onset of dermatomyositis and elevated serum IL-6 level after atezolizumab administration support the diagnosis of atezolizumab-induced dermatomyositis. Generally, patients with dermatomyositis are reported to show elevated serum levels of IL-6 compared with healthy controls (21, 22), but the increase is usually slight, and a prominent elevation of IL-6, as in this case, is rare.

In conclusion, we have presented a rare case of dermatomyositis associated with atezolizumab. Clinicians should note the rare manifestation of dermatomyositis after the administration of ICIs. The early detection of the characteristic erythema, myalgia, motor weakness, or elevated serum CK after the administration of ICIs may help achieve the early diagnosis of dermatomyositis due to ICI. The observation of muscle-related symptoms and serum CK levels after the administration of ICIs is also important for diagnosing other muscle-related irAEs including rhabdomyolysis and myositis. Consistent with previous studies suggesting a relationship between IL-6 and irAEs (17, 18), the serum levels of IL-6 in our case were prominently elevated in the acute phase of dermatomyositis. Further investigations will be required to clarify whether or not IL-6 is a useful biomarker for diagnosing irAEs or if it can function as a therapeutic target for irAEs (23).

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

References

1. Vaddepally RK, Kharel P, Pandey R, Garje R, Chandra AB. Review of indications of FDA-approved immune checkpoint inhibitors per NCCN guidelines with the level of evidence. Cancers (Basel) **12**: 738, 2020.
2. Brahmer JR, Lacchetti C, Schneider BJ, et al.; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol **36**: 1714-1768, 2018.
3. Postow MA, Sidlow R, Hellmann MD. Immune-related adverse events associated with immune checkpoint blockade. N Engl J Med **378**: 158-168, 2018.
4. Sheik Ali S, Goddard AL, Luke JJ, et al. Drug-associated dermatomyositis following ipilimumab therapy: a novel immune-mediated adverse event associated with cytotoxic T-lymphocyte antigen 4 blockade. JAMA Dermatol **151**: 195-199, 201.
5. Yamaguchi Y, Abe R, Haga N, Shimizu H. A case of drug-associated dermatomyositis following ipilimumab therapy. Eur J Dermatol **26**: 320-321, 2016.
6. Kudo F, Watanabe Y, Iwai Y, et al. Advanced lung adenocarcinoma with nivolumab-associated dermatomyositis. Intern Med **57**: 2217-2221, 2018.
7. Kadota H, Gono T, Shirai Y, Okazaki Y, Takeno M, Kuwana M. Immune checkpoint inhibitor-induced myositis: a case report and literature review. Curr Rheumatol Rep **21**: 10, 2019.
8. Shibata C, Kato J, Toda N, et al. Paraneoplastic dermatomyositis appearing after nivolumab therapy for gastric cancer: a case report. J Med Case Rep **13**: 168, 2019.
9. Kaji K, Fujimoto M, Hasegawa M, et al. Identification of a novel autoantibody reactive with 155 and 140 kD nuclear proteins in patients with dermatomyositis: an association with malignancy. Rheumatology (Oxford) **46**: 25-28, 2007.
10. Fujimoto M, Hamaguchi Y, Kaji K, et al. Myositis-specific anti-155/140 autoantibodies target transcription intermediary factor 1 family proteins. Arthritis Rheum **64**: 513-522, 2012.
11. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts). N Engl J Med **292**: 344-347, 1975.
12. Rittmeyer A, Barlesi F, Waterkamp D, et al.; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet **389**: 255-265, 2017.
13. Socinski MA, Jotte RM, Cappuzzo F, et al.; IMpower150 Study Group. Atezolizumab for first-line treatment of metastatic nonsquamous NSCLC. N Engl J Med **378**: 2288-2301, 2018.
14. Brahmer JR, Lacchetti C, Schneider BJ, et al.; National Comprehensive Cancer Network. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol **36**: 1714-1768, 2018.
15. Kishimoto T. IL-6: from its discovery to clinical applications. Int Immunol **22**: 347-352, 2010.
16. Lee DW, Gardner R, Porter DL, et al. Current concepts in the diagnosis and management of cytokine release syndrome. Blood **124**: 188-195, 2014.
17. Tanaka R, Okiyama N, Okune M, et al. Serum level of interleukin-6 is increased in nivolumab-associated psoriasiform dermatitis and tumor necrosis factor α is a biomarker of nivolumab recativity. J Dermatol Sci **86**: 71-73, 2017.
18. Naqash AR, Yang LV, Sanderlin EJ, Atwell DC, Walker PR. Interleukin-6 as one of the potential mediators of immune-related adverse events in non-small cell lung cancer patients treated with immune checkpoint blockade: evidence from a case report. Acta Oncologica **57**: 705-708, 2018.
19. Rotz SJ, Leino D, Szabo S, Mangino JL, Turpin BK, Pressey JG. Severe cytokine release syndrome in a patient receiving PD-1-directed therapy. Pediatr Blood Cancer **64**: 2017.
20. Sakakida T, Ishikawa T, Chihara Y, et al. Safety and efficacy of PD-1/PD-L1 blockade in patients with preexisting antinuclear antibodies. Clin Transl Oncol **22**: 919-927, 2020.
21. Gono T, Kaneko H, Kawaguchi Y, et al. Cytokine profiles in polymyositis and dermatomyositis complicated by rapidly progressive or chronic interstitial lung disease. Rheumatology **53**: 2196-2203, 2014.
22. Bilgic H, Ytterberg SR, Amin S, et al. Interleukin-6 and type I interferon-regulated genes and chemokines mark disease activity in dermatomyositis. Arthritis Rheum **60**: 3436-3446, 2009.
23. Stroud CR, Hegde A, Cherry C, et al. Tocilizumab for the management of immune mediate adverse events secondary to PD-1 blockade. J Oncol Pharm Pract **25**: 551-557, 2019.