Immunotherapy-intensified paraneoplastic dermatomyositis

Sir,

Atezolizumab is an immune checkpoint inhibitor that binds to programmed death-ligand 1, enhancing T-cell response to cancer. In parallel to anti-tumor immune response, it can promote autoimmunity. Dermatomyositis is an autoimmune disease characterized by proximal muscle inflammation, typical skin manifestations and systemic findings. In a subset of adults, it is associated with malignancies or it can be drug related.[1]

A 78-year-old man presented with a photodistributed erythematoviolaceous eruption, facial edema and painful erythema on the nailfolds [Figures1a-c]. He complained of proximal muscle weakness and myalgia. Musculoskeletal examination revealed grade 3/5 strength on abduction against resistance in the right shoulder and 2/5 in his left shoulder, as well as limited flexion of both hips.

He was on hydrocortisone, chlorthalidone, levothyroxine and clomethiazole for a traumatic hypopituitarism since the age of 16, olmesartan/amlodipine for hypertension and atorvastatin for dyslipidemia for more than two years. No new drugs had been introduced in the past year.

Two months earlier, he had been diagnosed with anaplastic small-cell lung cancer with metastases to brain, liver and bone (T4N3M1c Stage IVB). Chemoimmunotherapy with cisplatin, etoposide and atezolizumab was initiated as first line, receiving two doses. He remembered having at least two episodes of photodistributed erythema without muscle weakness months before the cancer diagnosis, not identifying a specific trigger.

Two weeks after atezolizumab induction, he presented erythema in sun-exposed areas that worsened with subsequent doses. By the time he was admitted for the third treatment cycle, erythema and muscle weakness were severe.

Laboratory findings showed elevated serum creatine kinase (creatine kinase: 8153 UI/L; reference range: ≤190), aldolase level of 45 UI/L (reference range: 0.1–7.6 UI/L), lactate dehydrogenase level of 578 UI/L (reference range: 135–225 UI/L) and serum creatinine 1.7 mg/dL (reference range: 0.7–1.3 mg/dL). Blood levels of aspartate aminotransferase (194 UI/L) and alanine aminotransferase (46 UI/L) were also increased. The complete blood count test revealed a neutrophilic leukocytosis (15.6×10^9, 93.9%). Urine analysis and sediment were normal.

Serologies showed strongly positive anti-transcriptional intermediary factor-1γ (TIF-1γ) and positive antinuclear antibody with negative anti-Jo1, anti nuclear matrix protein 2 and anti-double stranded DNA. Other myositis-related antibodies were negative. Skin biopsy [Figures 2a-c] was consistent with dermatomyositis. A magnetic resonance imaging of the shoulder and hip girdles showed intense muscle inflammation with edema.

Based on previous episodes of photodistributed erythema, characteristic clinicopathological and laboratory findings and chronological association between disease flares and atezolizumab, the patient was diagnosed with immune

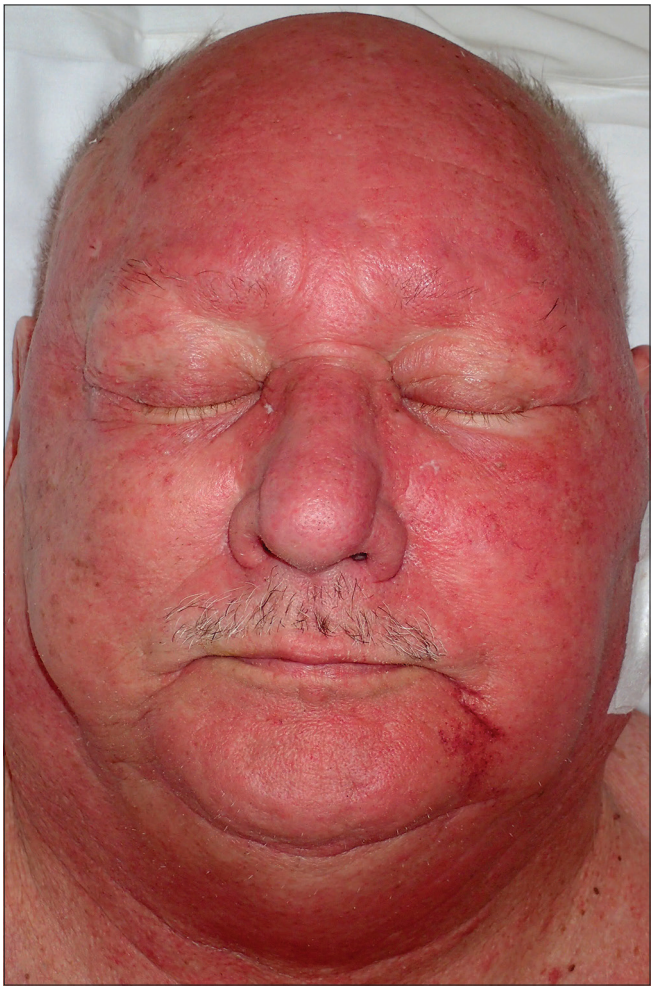

Figure 1a: Photodistributed erythema with eyelid edema

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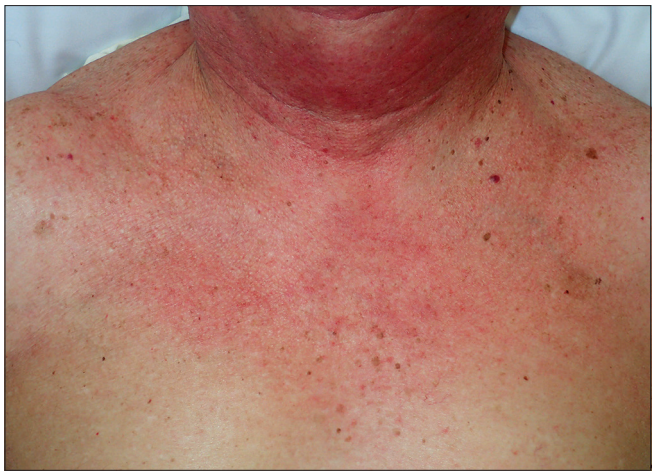

Figure 1b: V-shaped erythema affecting the upper chest

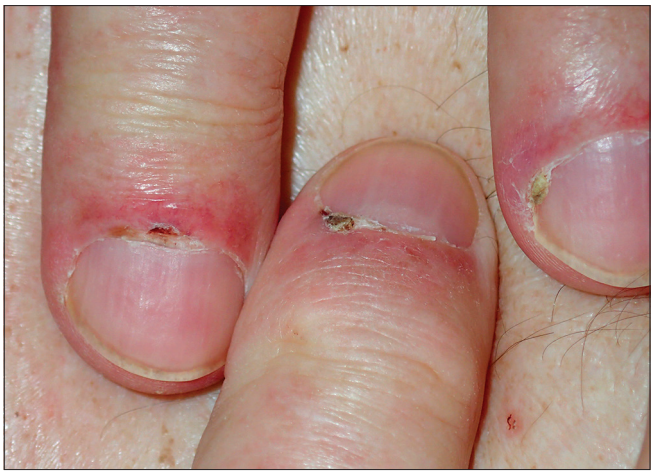

Figure 1c: Nailfold erythema in both hands

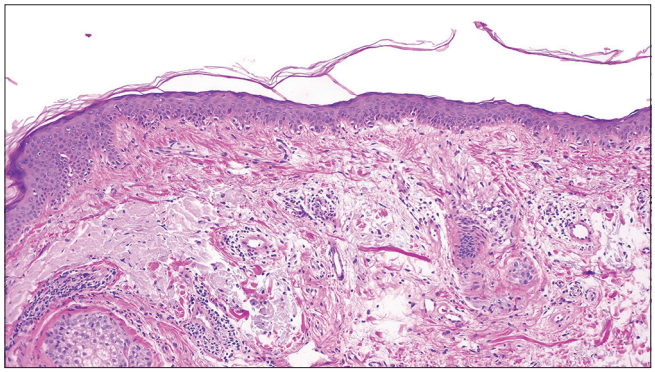

Figure 2a: Mild epidermal atrophy with vacuolar damage of the interface and perivascular lymphocytic infiltrate. A marked dermal edema along with mucin deposition (hematoxylin and eosin, 4×)

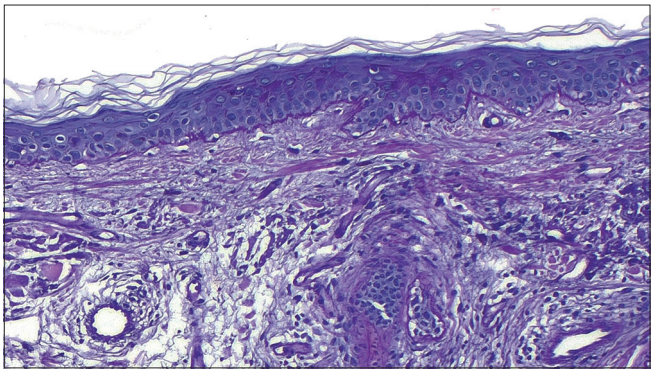

Figure 2c: Vacuolar interface dermatitis with a few necrotic keratinocytes and slight thickening of the basal membrane (periodic acid-Schiff, 10×)

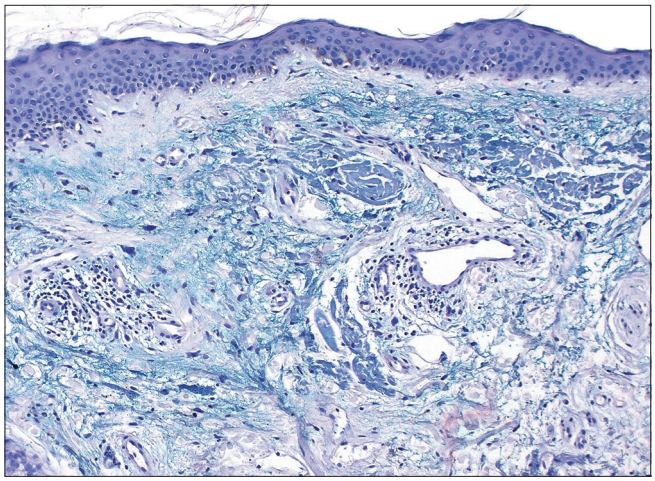

Figure 2b: Mucin deposition in the upper and lower dermis (colloidal iron staining, 10×)

checkpoint inhibitor intensified paraneoplastic dermatomyositis. Atezolizumab was discontinued, maintaining carboplatin and etoposide. He was started on oral prednisone (30 mg/day) and topical clobetasol once a day. During the follow-up visit after three weeks, clinical and laboratory findings were almost normal. Given good response, corticosteroids were maintained for three weeks with a tapering regime and double chemotherapy continued as scheduled. Even though rechallenge was not performed, the Naranjo probability scale showed a "probable" association with atezolizumab (six points).

Dermatomyositis is an idiopathic autoimmune myopathy that presents with proximal muscle weakness and characteristic skin findings including heliotrope rash, Gottron's papules and photodistributed erythema. It can be idiopathic, drug related (commonly associated with statins, hydroxyurea and penicillamine) or paraneoplastic. Up to 20% of adult patients have malignancies, most frequently lung cancer.[1]

Among patients with dermatomyositis, association to malignancies is more frequent when anti- transcriptional intermediary factor-1γ or anti-NXP-2 antibodies are present.[1]

While etiology is unknown, immune response with pro-inflammatory cytokines interleukin one alpha, interleukin one beta, tumor necrosis factor alpha, type 1 interferon, CD4+ and CD8+ lymphocytes have been identified.

Atezolizumab has been approved by the food and drug administration for the treatment of advanced stage non-small-

Table 1: Clinical and diagnostic findings of published cases of immunotherapy-related DM

Clinical and diagnostic findings	Sheik Ali *et al.*	Yamaguchi *et al.*	Kudo *et al.*	Liewluck *et al.*	Berger *et al.*	Yu *et al.*
Age	50	70	42	55	83	67
Sex	F	F	M	M	M	M
Primary disease	Melanoma	SCLC	Lung adenocarcinoma	NHL	Melanoma	Renal cell carcinoma
IT	Ipilimumab	Ipilimumab	Nivolumab	Pembrolizumab	Pembrolizumab	Nivolumab+ Cabiralizumab
Previous DM diagnosis	No	No	No	NS	No	No
Cycles until reaction	1	1	3	4	6	13
Skin findings	Photodistributed erythema. Heliotrope rash. Gottron's papules. Nailfold erythema.	Photodistributed erythema. Heliotrope rash.	Photodistributed erythema. Heliotrope rash. Gottron's papules. Nailfold erythema.	NS	Photodistributed erythema. Gottron's papules. Nailfold erythema.	Photodistributed erythema. Heliotrope rash. Gottron's papules. Nailfold erythema.
Muscle weakness	Proximal	Proximal, bulbar	Proximal	Proximal, bulbar	Proximal, paravertebral, bulbar	Absent
Highest CK (UI/L)	1854	794	137	72	1883	Normal
Aldolase (UI/L)	23	9.5	23.7	NS	15.5	Normal
LDH (UI/L)	NS	NS	738	NS	NS	NS
ANA	1/640	1/320	1/80	NS	1/1280	NS
Myositis antibodies	Anti-Jo1 negative	Anti-TIF1 alpha/gamma	Negative	Negative	Anti-TIF1 gamma	Negative
Other compatible diagnostic tests	MRI, MB	NS, SB	EMG, MRI	EMG, MRI, SB	EMG, MRI, MB, SB	NS, SB
Diagnosis	Drug induced	Drug induced	Drug induced	Drug induced	Drug induced	Drug induced
Treatment	CTC	CTC+IVIG	CTC	CTC	CTC+IVIG	CTC, MTX
Effect on IT	Discontinued	Discontinued	Discontinued	Discontinued	NS	Held
Tumor response to IT	PR	P	P	PR	PR	NR

Clinical and diagnostic findings	Kosche *et al.*	Shibata *et al.*	Sakakida *et al.*	Hinogami *et al.*	Our case
Age	63	71	70	74	78
Sex	M	M	M	M	M
Primary disease	Melanoma	Gastric cancer	NSCLC	Lung adenocarcinoma	Anaplastic SCLC
IT	Nivolumab	Ramucirumab≡Nivolumab	Atezolizumab	Pembrolizumab	Atezolizumab
Previous DM diagnosis	No	Erythema with ramucirumab	Paraneoplastic DM	No	No
Cycles until reaction	2	1	1	2	1
Skin findings	Photodistributed erythema. Heliotrope rash. Gottron's papules. Ragged cuticles.	Photodistributed erythema. Gottron's papules. Nailfold erythema.	Photodistributed erythema. Heliotrope rash.	Photodistributed erythema. Nailfold erythema and papules.	Photodistributed erythema. Nailfold erythema. Ragged cuticles.
Muscle weakness	Proximal	Proximal, bulbar	Proximal, bulbar	Proximal, paravertebral	Proximal
Highest CK (UI/L)	619	>1000	753	30	8153
Aldolase (UI/L)	56	>100	45.5	6.7	45
LDH (UI/L)	Normal	NS	1529	NS	578
ANA	1/640	1/80	1/80	NS	1/640
Myositis antibodies	Negative	Anti-TIF1 gamma	Anti-TIF1 gamma	Anti-TIF1 gamma	Anti-TIF1 gamma
Other compatible diagnostic tests	EMG, MB, SB	EMG, MRI	EMG	MRI, SB	MRI, SB
Diagnosis	Drug induced	Paraneoplastic DM (IT intensified)	Paraneoplastic DM (IT intensified)	Paraneoplastic DM (IT intensified)	Paraneoplastic DM (IT intensified)
Treatment	CTC+IVIG	CTC, SPT, IVIG, TCR	CTC	CTC+AZA	CTC
Effect on IT	Discontinued	Discontinued	Discontinued	Discontinued	Discontinued
Tumor response to IT	PR	P	P	PR	PR

DM: Dermatomyositis, F: Female, M: Male, SCLC: Small-cell lung cancer, NHL: Non-Hodgkin lymphoma, NSCLC: Non-small-cell lung cancer, CK: Creatine kinase, LDH: Lactate dehydrogenase, ANA: Antinuclear antibody, NS: Not specified, MRI: Magnetic resonance imaging, MB: Muscle biopsy, SB: Skin biopsy, EMG: Electromyography, IT: Immunotherapy, ≡: Transitioned to, CTC: Corticosteroid, SPT: Steroid pulse treatment, IVIG: Intravenous immunoglobulins, MTX: Methotrexate, AZA: Azathioprine, TCR: Tacrolimus, PR: Partial response, P: Progression, NR: No response

cell lung cancer. About 26.8% of patients treated with immune checkpoint inhibitor present immune-related adverse events, including dermatomyositis that can be severe, underlining their immunopotentiating mechanism of action.[2] We found only ten previous case reports of immune checkpoint inhibitor related dermatomyositis: two with anti-Cytotoxic T lymphocyte antigen four (CTLA)4 (ipilimumab), seven with anti-programmed cell death protein (PD)1 (four with nivolumab and three with pembrolizumab) and only one with anti-programmed death ligand (PDL)1 (atezolizumab) [Table 1].[3-12] Although the pathogenesis of immune checkpoint inhibitor related dermatomyositis is not fully understood, interferon γ enhanced CD4+ lymphocyte response to both self-antigens and tumor cells may play a role.[2] In fact, recent studies found better survival outcomes in patients with lung cancer presenting immune-related adverse events, even if their severity led to premature treatment discontinuation.[13]

Immune checkpoint inhibitor can relate to dermatomyositis as a drug-induced reaction[9] or as a flare of preexisting paraneoplastic dematomyositis.[11] In the previous case reports, symptoms developed between 1 and 13 treatment cycles with a median of 3.4 cycles [Table 1]. Importantly, immune checkpoint inhibitor had to be discontinued in 9 out of 11 cases given the intensity of the disease, along with systemic corticosteroids at 0.5–1.5 mg/kg/d in all cases [Table 1]. Additional treatments included intravenous immunoglobulins, azathioprine, methotrexate and tacrolimus. Topical potent or superpotent corticosteroids were added for skin symptoms [Table 1]. Although 8 out of 11 patients had positive antinuclear antibody test results [Table 1], it does not seem to predict the risk of developing an immune-related adverse events during treatment with immune checkpoint inhibitor.[11]

As this is a case report, a major limitation was the lack of ability to generalize our findings.

To conclude, dermatomyosits can be a serious complication during treatment with immune checkpoint inhibitor, requiring drug discontinuation and systemic corticosteroids in most patients. Clinicians should be aware of this potential complication of immunotherapy and closely monitor musculoskeletal and skin symptoms after drug administration.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest.

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