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INFLAMMATORY MUSCLE DISEASE (I LUNDBERG, SECTION EDITOR)

Immune Checkpoint Inhibitor-Induced Myositis: a Case Report and Literature Review

Hiroko Kadota[1] · Takahisa Gono[1] · Yuichiro Shirai[1] · Yuka Okazaki[1] · Mitsuhiro Takeno[1] · Masataka Kuwana[1]

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Abstract

Purpose of the Review We clarify clinical characteristics of patients with immune checkpoint inhibitor (ICI)-induced myositis.
Recent Findings In 13 of 15 cases with ICI-induced myositis, the type of malignancy was melanoma. Eight, 4, and 3 patients received anti-PD-1 alone, anti-CTLA4 alone, and a combination of those, respectively. The mean period to the onset of ICI-induced myositis from the initiation of ICI was 4 weeks. Myocarditis was a complication in five patients. Seven of the patients died. The causes of death were myocarditis in three patients, respiratory muscle paralysis in two patients, and cancer progression in two patients. In patients without myocarditis or respiratory muscle paralysis, the prognosis for myositis was favorable with normalization of the CK levels occurring upon the cessation of ICI and the administration of immunosuppressive agents.
Summary Myocarditis and respiratory muscle paralysis are the major causes of death as immune-related adverse events in patients with ICI-induced myositis.

Keywords Immune checkpoint inhibitor · Programed cell death-1 · Cytotoxic T lymphocyte antigen 4 · Autoreactive T cell · Myositis

Introduction

Polymyositis or dermatomyositis (PM/DM) is an idiopathic inflammatory myopathy (IIMs) that is caused by exaggerated activity of the autoimmune system. Myositis-specific autoantibodies (MSAs) are found in approximately 80% of patients with PM/DM [1]. PM/DM is also complicated with extramuscular manifestations such as interstitial lung disease (ILD), myocarditis, and arthritis. Cancer occurs more frequently in patients with PM/DM than in the general population [2]. Cancer-associated myositis (CAM) has been considered to be a paraneoplastic syndrome, and the anti-tumor immune response is involved in the development of myositis in CAM [3].

Recently, immune checkpoint inhibitors (ICIs) that target programmed cell death-1 (PD-1), such as nivolumab, or target cytotoxic T lymphocyte-associated protein 4 (CTLA4), such as ipilimumab, have improved the survival of patients with advanced malignancies, such as melanoma and non-small cell lung cancer [4, 5]. ICIs have the ability to potentiate T cell cytotoxicity against cancer cells [6]. Anti-PD-1 monoclonal antibodies selectively block the interaction between the PD-1 on T cells and the PD-ligand 1 (PD-L1) on the surface of the cancer cells in the tumor microenvironment. The blockade of PD-1-PD-L1 engagement restores T cell activation and proliferation and consequently enhances the anti-tumor immune response by the T cells. In contrast, CTLA4 is expressed transiently on activated T cells and usually serves to bind to CD80/86 on antigen-presenting cells (APCs) with greater affinity and avidity than CD28, which transmits a stimulatory signal to T cells. Thus, CTLA4 enables the outcompeting of CD28 for the binding of CD80/86 and subsequently inhibits T cell priming and activation. CTLA4 is also expressed constitutively on $Foxp3^+$ regulatory $CD4^+$ T cells and is involved in their inhibitory function. The blockade of CTLA4 accelerates the activation of T cells via CD28-CD80/86 signaling and, more directly, causes the inactivation and/or depletion of the regulatory T cells, which

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✉ Takahisa Gono
t-gono@nms.ac.jp

[1] Department of Allergy and Rheumatology, Nippon Medical School Graduate School of Medicine, 1-1-5 Sendagi, Bunkyo-ku, Tokyo 113-8603, Japan

consequently facilitates the T cell-mediated anti-tumor immune response.

ICIs also have the potential ability to stimulate the immune system against non-tumor cells, which leads to the development of immune-related adverse events (irAEs), such as dermatitis, endocrinopathies, colitis, hepatitis, and pneumonitis [7]. The pre-existence of autoimmune-mediated conditions is a risk factor for flare-ups of pre-existing autoimmune disease or the development of irAEs [8, 9•, 10•]. Recently, musculoskeletal disorders resembling rheumatoid arthritis and polymyalgia rheumatica have been reported to occur after treatment with ICIs [11•]. Additionally, myositis has also been reported to be one of the irAEs, and the incidences of myositis in patients treated with nivolumab or a combination of nivolumab and ipilimumab have been found to be 27 (0.15%) of 17,620 patients and 7 (0.24%) of 2974 patients, respectively [12••]. However, the detailed clinical characteristics of ICI-induce myositis remain unknown. There have never been articles on comprehensive literature review regarding myositis induced by several kinds of ICI including pembrolizumab (anti-PD-1), nivolumab (anti-PD-1), and ipilimumab (anti-CTLA4). Here, we would like to report a case of classic DM that was developed after the commencement of nivolumab, and show epidemiology, clinical characteristics, prognosis, and risk factors for mortality comprehensively by literature review regarding ICI-induced myositis.

Case Report

An 85-year-old Japanese woman was diagnosed with idiopathic interstitial pneumonia (IP) in May 2012. The high-resolution CT (HRCT) findings from the lungs revealed ground glass opacities (GGOs) accompanied by reticular shadows in the bilateral lower lobes, which indicated a non-specific IP (NSIP) pattern. At the time of diagnosis with idiopathic IP, she did not exhibit any symptoms related to IIMs, such as skin rashes, muscle weakness, or the elevation of myogenic enzymes. She was treated with methylprednisolone pulse therapy followed by oral prednisolone (PSL) at a dose of 1 mg/kg/day. After improvement of the IP, the PSL was tapered and discontinued in January 2013 without recurrence.

During the treatment of the IP, she was diagnosed with a malignant melanoma following a skin biopsy of a black spot on her right first toe in July 2012. The melanoma was surgically resected, and no additional treatments were applied. In August 2016, she developed advanced melanoma with metastases in the right nasal cavity and inguinal lymph nodes. Bleeding from the metastases in the nasal cavity was sustained, and hemostasis was difficult. However, at this time, she never complained of muscle weakness, skin rash, and respiratory symptoms, such as shortness of breath and dry cough. In October 2016, she received nivolumab at a dose of 3 mg/kg every two weeks for the metastatic melanoma. The sizes of the inguinal lymph nodes were reduced, and a response to the treatment with nivolumab was revealed. After the third administration of nivolumab, she experienced skin rashes on her face and extremities and muscle weakness and myalgia in the upper and lower proximal limbs with elevation of creatine kinase (CK; normal range 20–150) to 624 IU/L. Additionally, she also experienced shortness of breath on exertion and an elevation of serum KL-6. The HRCT before initiation of nivolumab revealed a reticular shadow, GGOs, and multiple cystic lesions away from the subpleural areas in the bilateral lower lobes predominantly in the left lobe of the lung. After the third administration of nivolumab, the HRCT scan revealed deterioration of the IP. Nivolumab was immediately discontinued, and she was referred to our department. Physical examination revealed superficial cervical lymph node enlargement and bilateral fine crackles at the lung base. She also exhibited a heliotrope rash, malar rash, shawl sign, and flagellate erythema on the back of the trunk, periungual erythema, mechanic's hand and Gottron sign on the fingers, elbow, and knee joint. She had muscle weakness of grades 4 of 5 in the upper limbs as assessed by manual muscle testing. Laboratory examinations revealed a serum CK level of 1743 U/L, a KL-6 level of 1353 U/mL (normal range < 500), and a positivity for antinuclear antibody with a homogeneous staining pattern at a titer of 1:80 in addition to cytoplasmic staining. She was diagnosed with classic DM with ILD.

Two months after the cessation of nivolumab, she stated that her myalgia and dyspnea had somewhat improved. The skin rashes associated with DM also improved. The CK and KL-6 levels were decreased to 922 U/L and 1056 U/mL, respectively. However, she still had difficulties with activities of daily living due to muscle weakness and dyspnea upon exertion. We treated her with PSL at 0.5 mg/kg/day in January 2017, which resulted in improvements in the muscle symptoms and skin rashes. The levels of CK declined into the normal range. The reticular shadow and GGO on the chest HRCT improved. However, 1 month later, the expansion of the melanoma that was refractory to DAVFeron (dacarbazine, nimustine, vincristine, and interferon beta) forced us to resume nivolumab. Subsequently, the disease status of the melanoma exhibited no progression, and the myositis, DM rashes, and ILD also remained unchanged with a maintenance dose of PSL of 10 mg/day.

A serum sample from the patient that was obtained before the introduction of nivolumab was available and was confirmed to be positive for the anti-KS antibody by RNA immunoprecipitation assay [13]. The antibody levels were measured at 3-time points, i.e., before nivolumab treatment, before PSL initiation, and 5 months after PSL treatment, using a commercial enzyme-linked immunosorbent assay for antibodies to aminoacyl tRNA synthetases (ARS) including Jo-1, EJ, PL-

12, PL-12, and KS [14], there were no obvious changes in the antibody levels from before to after the nivolumab treatment.

Literature Review

Methods We searched the literature dealing with cases of ICI-induced myositis using PubMed on October 1, 2017. "ICI-induced myositis" was defined as newly emerging systemic inflammatory myopathy involving the upper and/or lower limb muscles after the administration of ICI. Cases with focal myositis, such as orbital myositis, were excluded. We used the following keywords to search for articles in PubMed: "pembrolizumab," "nivolumab," "ipilimumab," "myositis," "myopathy/myopathies," "dermatomyositis," and "polymyositis." A total of 43 articles were initially selected; 30 articles were excluded because they were not in English writing ($n = 4$), lacked detailed case presentation ($n = 8$), and reported cases that were inconsistent with ICI-induced myositis ($n = 18$). Ultimately, we reviewed 14 cases of ICI-induced myositis as described in 13 articles [12••, 15–18, 19••, 20–26] and our case in Table 1.

Epidemiology The median age at onset of ICI-induced myositis was 73 years (range 50–89). The male and female cases were nearly equally distributed. The type of malignancy was melanoma in 13 cases, and one case each had a small cell lung carcinoma and an urothelial carcinoma. Eight (53%) patients received anti-PD-1 treatment alone, including pembrolizumab in 3 (20%) cases and nivolumab in 5 (33%). Four (27%) patients were treated with anti-CTLA4 ipilimumab alone. The remaining 3 patients (20%) were treated with a combination of nivolumab and ipilimumab. ICI-induced myositis was developed 4 ± 2 weeks (mean ± standard deviation) after initiation of ICI, and there were no apparent differences in the ICI treatment period before the onset of myositis according to the treatment regimen.

Skeletal Myopathy and Its Histology At least 11 patients (73%) exhibited proximal-dominant symmetrical limb weakness. Ptosis, ophthalmoplegia, dysphagia, and respiratory muscle paralysis were additionally reported in 6 (40%), 4 (27%), 7 (47%), and 6 (40%) patients, respectively. The median CK was 2812 IU/L (range 794–20,270). High CK levels (> 5000 IU/L) were detected in 6 patients (40%). Three patients (20%) developed rhabdomyolysis, and all of these patients were treated with a combination of nivolumab and ipilimumab.

Nine patients (60%) underwent skeletal muscle biopsy, and all except one (case 3) of these biopsies was adequate for histologic evaluation. The predominant histologic finding was endomysial infiltration of mononuclear cells, particularly $CD8^+$ T cells, in necrotic muscle fibers, which was observed in 6 cases. The remaining 2 cases exhibited almost no inflammation, which could potentially be explained by the fact that the biopsies were conducted after the initiation of the immunosuppressive therapies. Perifascicular atrophy, a typical muscle histological finding in DM, was not detected in any of the cases.

Myocarditis Myocarditis was reported in 5 patients (33%) who were treated with an anti-PD-1 agent. In case 2, a diagnosis of myocarditis was made at autopsy based on findings of patchy lymphohistiocytic infiltration with moderate cardiac myocyte hypertrophy and interstitial fibrosis. In two other fatal cases (cases 13 and 14), patchy lymphocytic infiltration in the myocardium, cardiac sinus, and atrioventricular nodes was confirmed by autopsy. In case 5, myocarditis was diagnosed based on marked CK-MB elevation, dyssynchrony of the left ventricle and apex as detected by echocardiography and a lack of clinically significant stenosis of the coronary artery, although histologic confirmation was not conducted. Cardiac conduction block was reported in cases 7, 13, and 14. All patients with myocarditis received an anti-PD-1 agent with or without combined ipilimumab.

Extra-Muscular Complications New-onset ILD was not reported in any of the patients; however, our case experienced an exacerbation of pre-existing ILD. Typical DM skin rashes were reported in 3 patients. Neither arthritis nor Raynaud's phenomenon were described in any of the patients.

Other irAEs Two patients developed myasthenia gravis (MG) with anti-AChR antibodies. In these 2 patients, ptosis progressed more rapidly than occurs in typical cases with MG. One patient (case 5) developed a myasthenic crisis that resulted in respiratory failure.

Treatment of ICI-Induced Myositis and Outcome The cessation of ICI and the administration of CS were simultaneously conducted in all patients with the exception of our case. In our case, the cessation of ICI alone resulted in partial improvements of the DM and ILD, but additional treatment with CS was required. Apheresis was performed in 6 patients (40%), including 4 for myositis, one for a myasthenic crisis, and 1 for both myositis and MG. Intravenous immunoglobulin was administered in 6 patients (40%), including 4 for myositis, one for a myasthenic crisis, and one for both myositis and MG. Infliximab was used in 2 patients, including one for myositis and one for both myositis and myocarditis. In terms of clinical outcomes, 7 cases (47%) died due to myocarditis ($n = 3$), respiratory muscle paralysis ($n = 2$), and cancer progression ($n = 2$). With the exceptions of the 4 patients with myocarditis who died, the treatment response of the myositis was generally favorable and included normalization of the CK level with 2 weeks to 4 months, although one case died of respiratory

Table 1 Clinical characteristics of ICI-induced myositis

Case [ref]	Age, gender	Type of tumor	Kind of ICI	Period from initiation of ICI to onset of myositis	Distribution of muscle involvement					Rhabdomyolysis	Muscle weakness scored by MMT	CK, UI/L
					Ptosis	Ophthalmoplegia	Dysphasia	Respiratory muscle paralysis	Lim weakness			
1 [15]	86 years, female	Melanoma	Pembrolizumab	3 weeks	+	+	–	–	Proximal upper and lower	–	N.A	1499
2 [16]	78 years, male	Melanoma	Pembrolizumab	5 weeks	+	+	+	+	Proximal upper and lower	–	N.A	1284
3 [17]	82 years, male	Melanoma	Pembrolizumab	2 weeks	+	+	+	+	Proximal lower	–	3 of 5	4670
4 [18]	84 years, male	Melanoma	Nivolumab	7 weeks	–	–	–	+	Proximal upper	–	4 of 5	2812
5 [19••]	80 years, male	Melanoma	Nivolumab	2 weeks	+	–	–	+	Proximal upper and lower	–	N.A	7740
6 [20]	75 years, female	Melanoma	Nivolumab	2 to 4 weeks	–	–	–	+	Proximal lower	–	N.A	1180
7 [21]	63 years, male	Melanoma	Nivolumab	2 weeks	–	–	+	–	Proximal upper	–	N.A	5148
8 (current case)	89 years, female	Melanoma	Nivolumab	6 weeks	–	–	–	–	Proximal upper	–	4 of 5	1800
9 [22]	51 years, female	Melanoma	Ipilimumab	3 to 6 weeks	–	–	+	–	Proximal and distal upper and lower	–	2 of 5	> 5000
10 [23]	50 years, female	Melanoma	Ipilimumab	1 to 4 weeks	–	–	–	–	Proximal upper and lower	–	4 of 5	1088
11 [24]	70 years, female	Melanoma	Ipilimumab	7 weeks	+	–	+	–	Proximal upper and lower	–	4 of 5	1200
12 [25]	70 years, female	Lung small cell carcinoma	Ipilimumab	3 weeks	–	–	+	–	Proximal upper and lower	–	N.A	794
13 [12••]	65 years, female	Melanoma	Nivolumab ipilimumab	2 weeks	N.A	N.A	N.A	N.A	N.A	+	N.A	17,720
14 [12••]	63 years, male	Melanoma	Nivolumab ipilimumab	3 weeks	N.A	N.A	N.A	N.A	N.A	+	N.A	20,270
15 [26]	73 years, male	Urothelial carcinoma	Nivolumab ipilimumab	3 weeks	+	+	+	+	Lower	–	N.A	13,710

Case [ref]	EMG	Muscle pathology	Myocarditis	ILD	DM	Other irAEs	Autoantibody	Treatment for myositis/ other irAEs	Outcome	Resumption of ICI	Efficacy of ICI against tumor
1 [15]	Myopathic change	Necrotic fiber with endomysial $CD8^+$ T cells infiltration	–	–	–	–	MSA and anti-AChR negative	PSL, PLEX	Nearly complete recovery in 1 month	–	Stable
2 [16]	Myopathic change	Necrotic fibers with mononuclear cells infiltration	+	–	–	–	Anti-AChR negative, anti-striated muscle	PSL, PLEX	Dead due to respiratory failure	–	Reduction
3 [17]	Myopathic change	Scarce striated muscle tissue insufficient to confirm the diagnosis	–	–	–	–	MSA and anti-AChR negative	PSL, IVIG, Plasmapheresis	CK levels normalized in 3 weeks, dead due to respiratory failure	–	N.A
4 [18]	N.A	N.A	–	–	–	–	N.A	PSL		–	N.A

Table 1 (continued)

Case [ref]	EMG	Muscle pathology	Myocarditis	ILD	DM	Other irAEs	Autoantibody	Treatment for myositis/ other irAEs	Outcome	Resumption of ICI	Efficacy of ICI against tumor
									CK levels normalized in 7 weeks		
5 [19••]	N.A	$CD4^+$ and $CD8^+$ cells infiltration	+	–	–	Myasthenia gravis	Anti-AChR*	PSL, IVIG, IA, PLEX, pyridostigmine	CK levels normalized in ~4 months	–	Stable
6 [20]	Myopathic change	N.A	–	–	–	–	N.A	PSL	CK levels normalized in 8 days	–	N.A
7 [21]	N.A	N.A	+	–	–	–	Anti-ARS, anti-SRP	PSL	Dead due to heart failure	–	N.A
8 (current case)	N.A	N.A	–	+	+	–	Anti-ARS*	PSL	CK levels normalized in ~2 months	+	Reduction
9 [22]	Myopathic change	Nectoric and regenerating fibers with endomysial macrophages and CD8+ T cells infiltration	–	–	–	–	N.A	IVIG, PSL	Weakness improved in 3 weeks	–	N.A
10 [23]	N.A	Atrophy of type 2 muscle fibers with no inflammation	–	–	+	–	ANA 640x, speckled pattern	PSL	CK levels normalized in 14 days	+**	Stable
11 [24]	Myopathic change	N.A	–	–	–	Myasthenia gravis	Anti-AChR	PSL, IVIG, PLEX, pyridostigmine	Weakness improved in 2 weeks	–	N.A
12 [25]	N.A	N.A	–	–	+	–	Anti-TIF1-γ	PSL, IVIG	DM improved, dead due to progression of cancer	–	N.A
13 [12••]	N.A	Macrophages and predominant CD8+ T cells infiltration	+	–	–	–	N.A	PSL	Dead due to VT	–	N.A
14 [12••]	N.A	Macrophages and predominant CD8+ T cells infiltration	+	–	–	–	N.A	PSL, IFX	Dead due to cardiac arrest	–	N.A
15 [26]	N.A	Mild degeneration muscle fiber without $CD3^+$ cells infiltration	–	–	–	–	Anti-striated muscle*	PSL, IFX, IVIG, Plasmapheresis	Weakness improved in 3 weeks, dead due to progression of cancer	–	N.A

ICI, immune checkpoint inhibitor; *MMT*, manual muscle testing; *CK*, creatine kinase; *EMG*, electromyogram; *MRI*, magnetic resonance imaging; *ILD*, interstitial lung disease; *DM*, dermatomyositis; *irAEs*, immune-related adverse events; *N.A.*, not available; *AChR*, acetylcholine receptor; *ARS*, aminoacyl-tRNA synthetase; *SRP*, signal recognition particle; *TIF1-γ*, transcription intermediary factor 1-γ; *PSL*, prednisolone; *PLEX*, plasma exchange; *IVIG*, intravenous immunoglobulin; *IA*, immunoadsorption; *IFX*, infliximab

*Autoantibodies were pre-existing before initiation of ICI, **ICI resumed after development of DM, then DM relapsed

muscle paralysis (case 3). The ICI resumed in 2 patients (13%) including our case. In another patient (case 10), the resumption of ipilimumab led to the recurrence of symptoms associated with DM.

Association with ICI Efficacy Against Tumors We obtained data regarding efficacy of ICIs against tumors from 5 of 14 cases who exhibited ICI-induced myositis. Reductions in tumor size and stable diseases after the initiation of an ICI were observed in 2 and 3 patients, respectively. The efficacy of ICI treatment against the tumors seemed to be found in all of the 5 patients.

MSAs and Other Autoantibodies The presence of MSAs was reported in 3 patients and included the coexistence of anti-ARS and anti-signal recognition particle (SRP) antibodies in case 7, anti-ARS antibody in our case, and anti-TIF1-γ antibody in case 12. Another patient (case 10) was reported to be positive for anti-nuclear antibody (ANA) and exhibited a speckled pattern at a titer of 1:640, but the specificity was not described. All 3 patients who developed typical DM rashes had MSA or high-titer ANA. Anti-AChR and anti-striated muscle autoantibodies were reported in two patients each. Of these 8 patients with autoantibodies, 3 patients were reported to have autoantibodies before ICI introduction, including anti-AChR in case 5, anti-ARS in our case, and anti-striated muscle in case 15.

Discussion

We report a case of classic DM with ILD in association with anti-ARS antibody after the initiation of ICI and conducted a literature review of patients with ICI-induced myositis. The detailed review of a total of 15 patients with ICI-induced myositis, including our case, revealed that ICI-induced myositis developed shortly after the introduction of ICI irrespective of the agents employed. Additionally, the clinical presentation of ICI-induced myositis can be divided into two distinct clinical subsets, i.e., cases involving the de novo onset of an immune attack on skeletal and cardiac muscles as well as the neuromuscular junction as one of the irAEs and cases involving the development of full-blown IIMs in individuals with pre-existing autoimmune conditions. In the former subset, the clinical presentations are quite different from that of IIMs. Specifically, the most remarkable point is the difference in the distribution of muscle involvement. Ptosis and/or ophthalmoplegia, which are rarely observed in patients with IIMs, were reported in 6 patients. Two of these 6 patients had concomitant MG and anti-AChR antibodies, and additional two patients were positive for anti-striated muscle autoantibody, which is associated with MG complicated by myositis and myocarditis [24], although MG was not definitely diagnosed. None of the 6 patients with ptosis and/or ophthalmoplegia had MSA. Respiratory muscle paralysis was also found in 4 patients with ptosis and/or ophthalmoplegia. Therefore, patients with ptosis, ophthalmoplegia, and/or respiratory muscle paralysis might be related to an MG component. Additionally, myocarditis was often accompanied by ICI-induced myositis, although apparent cardiac involvement was less frequent (~10%) in the patients with IIM [25]. Myocarditis developed abruptly and progressed rapidly, was associated with concomitant cardiac conduction block, and led to death in 4 of 5 patients. Together, these clinical features suggest that, compared with IIMs, skeletal and cardiac muscle involvement is more severe and develops more rapidly in ICI-induced myositis. Interestingly, the skeletal muscle involvement responded favorably to ICI termination and CS treatment, although myocarditis and respiratory muscle paralysis were two major causes of death. These features together indicate that the majority of ICI-induced myositis cases could be irAEs that are distinct from IIMs as suggested by the abrupt onset and rapid progression of the disease, the unique clinical presentation, such as the coexisting MG and myocarditis, and the lack of MSAs.

In contrast, there could be a subset of ICI-induced myositis that mimics IIM and is characterized by the absence of atypical muscular involvement (including ptosis, ophthalmoplegia, respiratory muscle paralysis, rhabdomyolysis, and fatal myocarditis), the presence of DM skin rashes, and the exacerbation of pre-existing ILD and MSAs; although the occurrence of this subset is infrequent. In our case, ILD in association with anti-ARS antibody was already present before the initiation of nivolumab. At this time, our patient exhibited no apparent DM features, such as typical skin rashes and inflammatory myopathy, consistent with the clinical diagnosis of IP with autoimmune features (IPAF) or antisynthetase syndrome [27]. This subset featuring IIM might just be CAM because one of the patients was positive for the anti-TIF1-γ antibody, which is strongly associated with CAM [28]. Actually, it is difficult to distinguish between ICI-induced myositis and CAM, but we believe that the use of ICI somehow contributed to the onset of the disease because of the abrupt onset after the initiation of ICI and the improvement due to the termination of ICI.

The clinical presentations of ICI-induced myositis were similar between the patients who were treated with anti-PD-1 and anti-CTLA4 biologics, but there were some potential differences, e.g., myocarditis was observed exclusively in the patients who were treated with anti-PD-1 biologics, and rhabdomyolysis was observed exclusively in the patients who were treated with the combination of anti-PD-1 and anti-CTLA4 biologics. However, the number of patients in the literature is too small to draw a definitive conclusion at this moment.

Because we propose that ICI-induced myositis can be divided into two distinct clinical subsets, the underlying pathophysiology might be different between the two subsets as illustrated in Fig. 1. The de novo onset of an immune attack of the skeletal and cardiac muscles is supposed to be one of the irAEs (Fig. 1a). It has been suggested that tumor-reactive T cells, particularly $CD8^+$ cytotoxic T cells, are stimulated by the suppression of immune checkpoint signals and develop an autoaggressive response that results in the development of irAEs [12••, 19••]. The skeletal muscle pathology of ICI-induced myositis included the infiltration of mononuclear cells, especially $CD8^+$ T cells, into the muscle fibers, which mimics the pathohistology of PM [29]. Similar histologic findings in the myocardium were also reported in patients who developed myocarditis. In these cases, identical clonal $CD8^+$ T cells were found in the skeletal muscle, myocardium, and cancer cells [12••], which indicates that the same T cell repertoire has the ability to attack not only tumor cells but also skeletal muscles and the myocardium. The activation and expansion of these anti-tumor T cells by treatment with ICIs and the resultant diversification of the immune responses to autoantigens are proposed as a hypothesis for the initiation of the irAEs [30]. Therefore, the blockade of PD-1-PD-L1 and/or CTLA4-CD80/86 signaling might lead to the activation of pre-existing clonal $CD8^+$ T cells associated with anti-tumor response and induce the diversification of their recognition to skeletal and cardiac muscles. Because the duration between the initiation of ICI and the development of ICI-induced myositis was only an average of 4 weeks, it is likely that a pathogenic T cell repertoire is already present and is activated by the administration of ICIs.

In contrast, in cases involving the development of full-blown IIMs in individuals with pre-existing autoimmune conditions, treatment with ICIs might induce the activation of underling autoimmune disease-predisposed autoreactive T cells and exaggerate the pre-existing autoimmune disease (Fig. 1b). In this subset of patients, autoantibodies are present before ICI use, and the majority of these patients developed DM in which $CD4^+$ T cells and B cells were more closely involved in the pathophysiology [29]. In our case, the anti-KS antibody titers did not change remarkably after the initiation of nivolumab. This finding indicated that B cells are not closely involved in the development of DM. Blockade of PD-1-PD-L1 engagement by nivolumab might stimulate IIM-predisposed T cells and induce skin rashes and myositis as well as ILD.

In our literature of review, the number of patients is too small to draw definitive conclusions. In the future, all patients treated with ICI should be prospectively enrolled in studies, and we need to clarify clinical characteristics and immunological conditions of ICI-induced myositis using data from a large cohort.

Conclusions

The clinical characteristics of ICI-induced myositis can be divided into two subsets: the de novo onset of myositis as

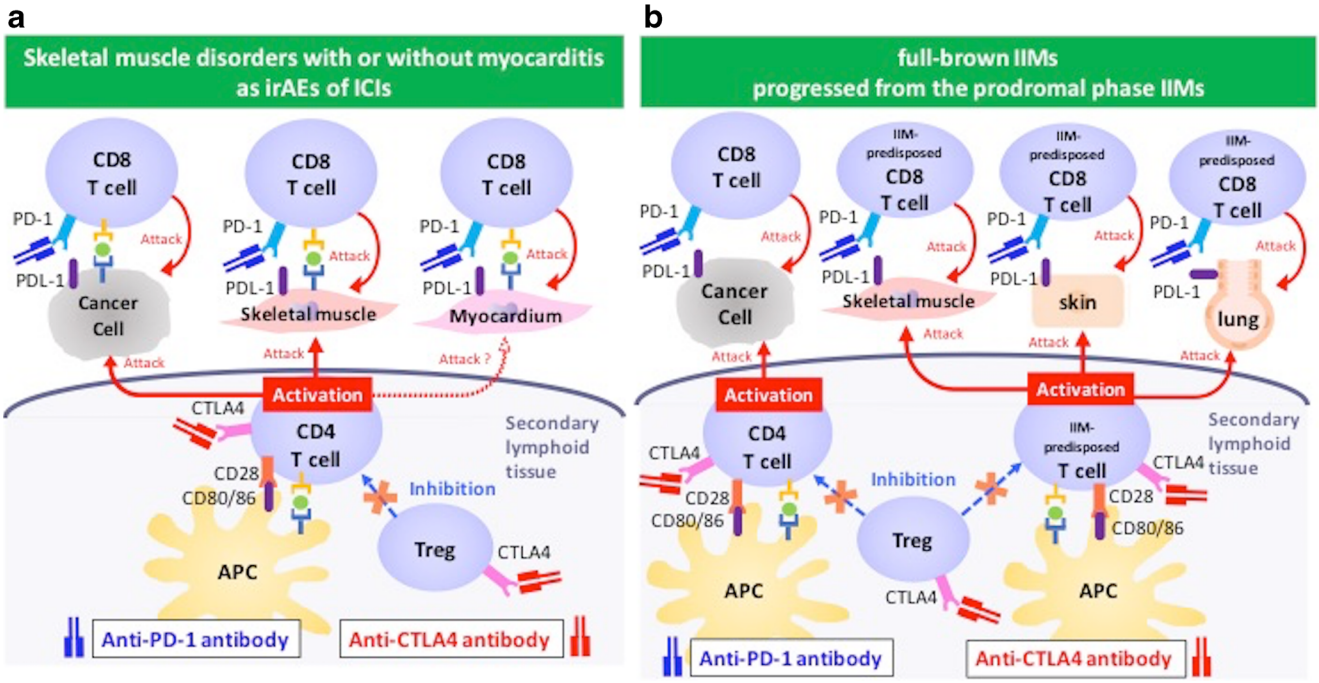

Fig. 1 Presumptive pathophysiology regarding ICI-induced myositis. **a** De novo-onset skeletal muscle disorders as irAEs due to ICIs. **b** Development of underlying autoimmune diseases, such as full-blown IIMs, from the prodromal phase due to ICIs. irAEs, immune-related adverse events; ICI, immune checkpoint inhibitor; IIM, idiopathic inflammatory myopathies; PD-1, programmed cell death-1; PDL-1, programmed death-ligand 1; CTLA4, cytotoxic T-lymphocyte-associated protein 4; APC, antigen-presenting cell; Treg, regulatory T cell

one of the irAEs and the development of IIMs. Myocarditis and respiratory muscle paralysis are the major causes of death as irAEs in patients with ICI-induced myositis, and these conditions are less frequently observed in full-blown IIMs.

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Compliance with Ethical Standards

Conflict of Interest The authors declare no conflicts of interest in this work. Outside the submitted work, Kadota H, Shirai Y, and Okazaki Y have nothing to disclose. Gono T, Takeno M, and Kuwana M have relevant financial activities outside the submitted work as follows: Gono T, personal fees from Astellas Pharma, personal fees from Chugai Pharmaceutical, personal fees from Daiichi sankyo, personal fees from Janssen Pharmaceutical, personal fees from Mitsubishi Tanabe Pharma, personal fees from Ono Pharmaceutical; Takeno M, personal fees from Celgene, personal fees from Tanabe-Mitsubishi, Co, personal fees from Eizai, Abbbie, grants from Novortis; Kuwana M, grants and personal fees from Chugai Pharmaceutical, grants and personal fees from Mitsubishi Tanabe Pharma, grants and personal fees from Ono Pharmaceutical, grants and personal fees from Pfizer, personal fees from Janssen Pharmaceutical, grants and personal fees from Astellas Pharma, grants and personal fees from Esai, personal fees from Boehringer Ingelheim, personal fees from Bayer, personal fees from Corbus, personal fees from Reata.

Ethics Approval and Consent to Participate This study was approved by the ethics committee of Nippon Medical School Hospital (approval number 28-12-680) and was conducted in accordance with the Declaration of Helsinki. Our patient provided informed consent to participate in this study and consent for the use of the data.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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