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Neuromuscular Complications of Programmed Cell Death-1 (PD-1) Inhibitors

Justin C. Kao[1] · Adipong Brickshawana[2] · Teerin Liewluck[3]

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Abstract

Purpose of Review In recent years, immune checkpoint inhibitors have been increasingly used in patients with metastatic cancers with favorable oncological outcomes; however, there have also been increasing number of cancer survivors who have developed immune-related adverse events. Little is known about PD-1 inhibitor-associated neuromuscular complications.

Recent Findings Neuromuscular disorders are the most common neurological complication reported in PD-1 inhibitor-treated patients. Myasthenia gravis, immune-mediated myopathies, and Guillain-Barre syndrome are among commonly reported immune-related neuromuscular complications. HyperCKemia occurs frequently in patients with PD-1 inhibitor-associated myasthenia gravis, indicating coexisting myopathies or myocarditis. Oculobulbar weakness is a unique and common presentation of PD-1 inhibitor-associated immune-mediated myopathies with or without concomitant myasthenia gravis. High-dose steroid monotherapy may be associated with clinical deterioration in some patients with PD-1 inhibitor-associated myasthenia gravis, immune-mediated myopathies, or Guillain-Barre syndrome.

Summary PD-1 inhibitor-associated neuromuscular complications have some characteristic features compared to their idiopathic counterparts. Although steroid monotherapy is commonly used in non-neuromuscular autoimmune disorders triggered by anti-PD-1 therapy, this may lead to unfavorable outcomes in some patients with PD-1 inhibitor-associated neuromuscular complications.

Keywords Myasthenia gravis · Myositis · Neuropathy · Nivolumab · Pembrolizumab · Programmed cell death-1 (PD-1) inhibitors

Introduction

Cancer Immunotherapy

The idea of utilizing a patient's own immune system to fight cancer can be traced back to at least the 1890s when William Coley first noticed that cancer patients with post-surgical infection tend to have better clinical outcomes [1]. Cancer immunotherapy has progressed considerably since then, partly thanks to our improved understanding of the factors that promote or inhibit T cell responses [2]. The balance between promotion and inhibition of T cell responses help prevent the development of autoimmune diseases. Immune checkpoints are inhibitory molecules that play a key role in dampening the T cell responses, promoting self-tolerance, and preventing autoimmunity. Two well-characterized immune checkpoints are cytotoxic T-lymphocyte-associated protein-4 (CTLA-4) and programmed cell death 1 (PD-1) [2, 3]. After receiving the initial activating signals in secondary lymphoid organs, T cells upregulate CTLA-4, which modulates the magnitude of the initial T cell response. In contrast, PD-1 suppresses T cell response in peripheral tissues and plays a key role in peripheral tolerance [3] as shown in Fig. 1.

PD-1 is expressed by both activated CD4+ and CD8+ T cells, and its expression is particularly high in chronically activated T cells (often referred to as "exhausted" T cells) and autoreactive T cells [4, 5]. Its ligands, PD-L1 and PD-L2, are expressed in a wide variety of tissues and are thought to protect these tissues from damage during chronic

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✉ Teerin Liewluck
liewluck.teerin@mayo.edu

[1] Department of Neurology, Auckland City Hospital, Auckland, New Zealand

[2] Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine, Bronx, NY, USA

[3] Department of Neurology, Mayo Clinic, 200 First Street SW, Rochester, MN, USA

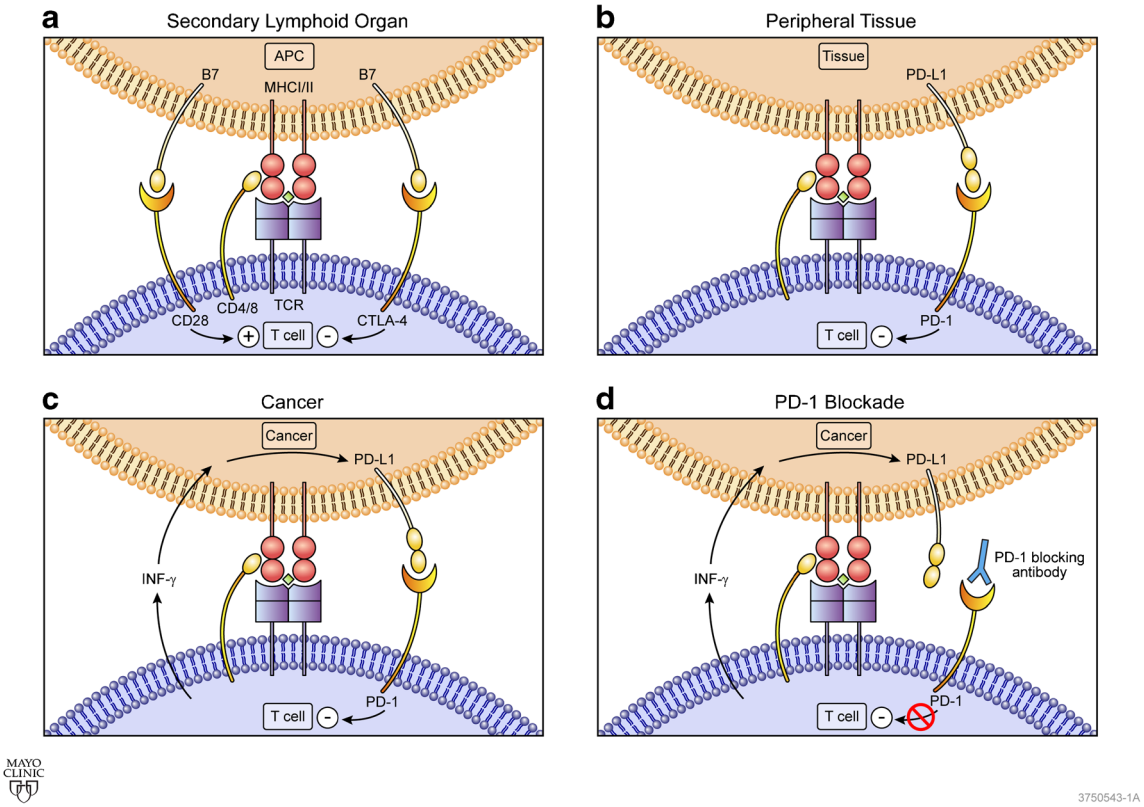

Fig. 1 Immune checkpoints during different aspects of immune response. **a** T cell receiving activating signals in secondary lymphoid organ: signal 1—T cell receptor (TCR) binding to cognate peptide/MCH complex, and signal 2—interaction between B7 with CD28. Upregulation of CTLA-4 following T cell activation provides inhibitory signal that modulates T cell response. **b** PD-1 interaction with PD-L1 provides an inhibitory signal, limiting inflammation and autoimmunity in peripheral tissue. **c** Cancer cells can also upregulate PD-L1 in response to INF-γ secretion, providing inhibitory signal to T cells and allowing cancer cells to evade antitumor immunity. **d** PD-1 blocking antibody blocks PD-1 suppression, unleashing antitumor immune response. (*APC* antigen presenting cell)

inflammation and from autoreactive T cells [4]. In cancer, this protective pathway can be hijacked. Cancer cells can upregulate PD-L1 in response to INF-γ secreted by immune cells, and subsets of tumor-infiltrating T cells are known to express PD-1 as a consequence of chronic stimulation [6, 7]. Therefore, one of the ways cancer cells evade the immune system is by utilizing the PD-1 pathway to suppress an antitumor immune response [7].

Understanding the role of the immune checkpoints, CTLA-4 and PD-1, has led to the development of immune checkpoint inhibitors with the aim of unleashing this antitumor immune response. These checkpoint inhibitors have been a major breakthrough in cancer immunotherapy due to their ability to cause durable regression of many different types of established cancers [8•]. Ipilimumab is the first CTLA-4 blocking antibody approved for treatment of metastatic melanoma in 2011 [8•]. The PD-1 blocking antibodies, nivolumab (first human trial in 2006) and pembrolizumab (first human trial in 2011), are now approved for use in multiple cancers including melanoma, non-small cell lung cancer, and head and neck cancer [8•]. As this list of indications continues to grow, the use of immune checkpoint inhibitors is becoming increasing more prevalent, as well as the rise of reported cases with immune-related adverse events, highlighting the need to study their side-effects and the management of possible adverse outcomes.

Immune-Related Adverse Events of PD-1 Inhibitors

Blockade of an immune checkpoint, such as PD-1, can not only unleash anti-tumor immune response but can also lead to autoimmunity, possibly by blocking PD-1 suppression of autoreactive T cells [4, 9]. Fortunately, most common side-effects are constitutional, but severe adverse events can be seen in 5–10% of patients treated with nivolumab or pembrolizumab [10, 11]. Neurological complications have been reported in 1–4.2% of patients treated with PD-1 inhibitors [12••, 13••, 14], which is less common compared to dermatologic, endocrine, gastrointestinal, or rheumatologic complications, each of which was reported in approximately 10–15% of PD-1 inhibitor-treated patients [14]. Among PD-1 inhibitor-associated neurological complications, neuromuscular disorders are

the most common, accounting for 60–75% [12••, 13••]. Myasthenia gravis is the most frequently reported PD-1 inhibitor-associated neuromuscular complication in the literature, followed by immune-mediated myopathies and Guillain-Barre syndrome. In our cohort, the estimated frequency of myasthenia gravis, immune-mediated myopathies, and Guillain-Barre syndrome in PD-1inhibitor-treated patients is 0.15, 0.76, and 0.3%, respectively [12••, 15••]. Although neuromuscular complications are relatively uncommon compared to immune-mediated complications affecting other systems, these are potentially fatal. Early recognition and prompt treatment may help reduce morbidity and mortality rates among these patients. Herein, we provide a comprehensive review of neuromuscular complications of anti-PD-1 immunotherapy and suggest a diagnostic algorithm and treatment considerations (Table 1).

Neuromuscular Complications of PD-1 Inhibitors

Neuromuscular Junction Disorders

Myasthenia gravis is the most commonly reported PD-1 inhibitor-associated neuromuscular complications. At least 33 patients (18 nivolumab, 14 pembrolizumab, and 1 combined nivolumab and ipilimumab) were described [13••, 15••, 16–36, 37••]. Suzuki and colleagues reported a series of 12 patients with nivolumab-associated myasthenia gravis, 3 of whom were previously reported in English literature [20, 25, 28, 37••], while others described one or two individual cases. The frequency of myasthenia gravis was estimated at 0.12% of nivolumab-treated patients in Japan [37••] and 0.15 to 0.2% of all PD-1 inhibitor-treated patients in America or Europe, respectively [13••, 15••]. It has been suggested that there might be a higher incidence of PD-1 inhibitor-associated

Table 1 Common PD-1 inhibitor-associated neuromuscular complications

Features	Myasthenia gravis	Immune-mediated myopathies	Guillain-Barre syndrome
Frequency among PD-1 inhibitor-treated patients	0.12–0.2%	0.58–0.76%	0.2–0.3%
Number of PD-1 inhibitor treatments prior to the onset of neuromuscular complications (median)	1–4 (2)	1–9 (2)	2–18 (4.5)
Duration (weeks) between initiation of PD-1 inhibitors and symptom onset (median)	2–15 (5)	2–15 (3)	4–68 (12)
Common associated autoimmune disorders (%)	HyperCKemia* (87%) Myocarditis (25%)	Myasthenia gravis (45%) Myocarditis (29%)	–
Diagnostic workup			
1. Confirmatory tests	1. AChR, MuSK, and LRP4 antibodies 2. EMG, including repetitive nerve stimulation and/or single fiber EMG	1. Creatine kinase 2. Myositis and necrotizing autoimmune myopathy antibodies 3. EMG 4. Muscle biopsy	1. EMG 2. CSF studies 3. Ganglioside antibodies
2. Surveillance for common associated autoimmune disorders	1. Creatine kinase and troponin I level 2. EKG or Holter monitor, echocardiogram, and cardiac monitor especially if creatine kinase or troponin I level is elevated 3. Muscle biopsy and serology testing (see under immune-mediated myopathies) if creatine kinase level is elevated	1. Repetitive nerve stimulation and/or single fiber EMG 2. AChR, MuSK, and LRP4 antibodies, especially if repetitive nerve stimulation or single fiber EMG is abnormal 3. Troponin I level 4. EKG or Holter monitor, echocardiogram, and cardiac monitor	–
Initial treatment considerations**	1. Avoid high-dose steroid monotherapy 2. IVIG or plasma exchange together with steroid in patients with severe weakness or myasthenic crisis	1. Avoid high-dose steroid monotherapy 2. IVIG or plasma exchange together with steroid	1. IVIG or plasma exchange 2. Steroid if no improvement with IVIG or plasma exchange
Mortality rate	30.3%	25%	12.5%

*Among 19 patients, 5 had biopsy-proven immune-mediated myopathies, 2 had biopsy-proven myocarditis, and 1 had biopsy-proven immune-mediated myopathies and myocarditis

**Long-term follow-up in these patients are required to determine the ongoing use of immunosuppressants

myasthenia gravis in Asia compared to the Western countries [35]. However, only half of the reported patients were from Asia [20, 25, 28, 32–35, 37••].

The exact mechanism for these PD-1 inhibitor-associated myasthenia gravis remains largely unknown. It is possible to speculate that myasthenia gravis is triggered by unleashed autoreactive CD4+ T cells providing help to autoreactive B cells [37••]. However, there have also been reports of PD-1 expression on B cells [38, 39]. Therefore, a direct role of PD-1 inhibitors on B cells cannot be excluded. In PD-1 inhibitor-treated patients, myasthenia gravis occurred de novo in approximately two thirds of these cases, while the remaining patients had pre-existing disease or were [25, 28, 32–35, 37••] seropositive for acetylcholine receptor (AChR) antibodies predated the PD-1 inhibitor therapy. Two thirds of patients were acetylcholine receptor (AChR) antibody-positive. The mean titer of AChR antibodies was 6.2 nM (range, 0.05 to 28 nM; median, 0.86) in 15/24 individual reported cases and 6.8 nM in 10/12 cases reported by Suzuki et al., which is approximately 8.5 times lower than what was observed in patients without PD-1 inhibitor exposure [37••]. None of the patients were seropositive for MuSK antibodies.

In many of these patients, the diagnosis of myasthenia gravis was based on the clinical features, plus or minus the presence of AChR antibodies alone, without supporting electrodiagnostic studies. Electrodiagnostic studies were only reported in 19/33 cases and positive in 10 out of these 19 cases (53%), including 5 patients with abnormal decrement on low-frequency repetitive nerve stimulation [21, 26, 30, 37••] and 5 patients with increased jitter on single fiber EMG [23, 24, 34, 36, 37••]. Given cases of PD-1 associated myopathy with ptosis, ophthalmoparesis and bulbar weakness mimicking myasthenia gravis have also been reported [15••, 40], it is difficult to know with certainty in some of these cases how much of the patient's presentation was due to a defect in neuromuscular transmission versus myopathy, especially in those seronegative cases with hyperCKemia.

Among 24 individual reported patients, myasthenic symptoms occurred after the mean and median of 2.4 and 2 doses of PD-1 inhibitors (range, 1–4), which is similar to what was reported by Suzuki et al. [37••]. Duration between symptom onset and the initiation of anti-PD1 therapy ranged from 2 to 15 weeks (median, 5 weeks). Of the 4 patients with pre-existing myasthenia gravis, prior to the initiation of anti-PD-1 therapy their myasthenic symptoms were well-controlled with immunosuppressants in 3 patients, including azathioprine [16], mycophenolate mofetil [18], or alternate day steroid [20], and required no immunosuppressant in 1 patient [21]. A couple of patients had their dose of immunosuppressants reduced before the commencement of PD-1 inhibitors. The presence of other underlying autoimmune diseases on the other hand was very rarely mentioned in these case reports. One patient had rheumatoid arthritis [21] and the other had subclinical autoimmune thyroid disease [28].

Myasthenia gravis arising in the setting of PD-1 inhibitor therapy appears to have some unique characteristics. First, myasthenic crisis or respiratory failure requiring ventilatory support in particular was common and occurred in 12/24 (50%) individual reported cases [15••, 16, 18, 19, 25–30, 33, 35] and in 5/12 (42%) patients reported by Suzuki et al. [37••]. This is 7 times higher than what was reported in PD-1 inhibitor-naïve myasthenia gravis patients [37••]. Only 18% (6/33) of PD-1-associated myasthenia gravis patients had pure ocular form [17, 22, 31, 36, 37••]. Myasthenia gravis patients who received PD-1 inhibitor therapy are also 2.6 to 3 times more likely to develop bulbar weakness compared to patients who did not receive PD-1 inhibitors [37••] . Second, creatine kinase elevation was common in PD-1 inhibitor-associated myasthenia gravis, suggestive of concomitant muscle or cardiac diseases. Creatine kinase level was reported in 23/33 cases and was elevated in 20 (87%) [13••, 15••, 20, 24–29, 32–35, 37••], ranging from mild elevation to as high as 12,119 U/L. The mean CK level was 4799 IU/L in PD-1 inhibitor-treated patients compared the mean of 119 IU/L in patients without PD-1 inhibitor exposure [37••]. Asymptomatic or paucisymptomatic elevation of CK level may precede myasthenic symptoms [20, 28]. Of 20 patients with hyperCKemia, only 6 had biopsy-proven myopathy (5 inflammatory myopathy and 1 necrotizing autoimmune myopathy) [15••, 25, 35, 37••] and 3 had biopsy-proven myocarditis [25, 37••]. One patient had both inflammatory myopathy and myocarditis [25, 37••]. The coexistence of myasthenia gravis and inflammatory myopathy has also been described in myasthenia gravis prior to the cancer immunotherapy era, but at a much lower frequency (0.65–2.3%) [41, 42]. The frequency of myocarditis in PD-1 inhibitor-naïve myasthenia gravis range from 0 to 0.35% compared to 25% in PD-1inhibitor-treated patients [37••, 41]. Patients with hyperCKemia appear more likely to deteriorate to crisis requiring ventilatory support. Among 15 patients who developed respiratory failure, 10 patients had hyperCKemia [15••, 25, 26, 28, 29, 33, 35, 37••], 1 patient had normal CK [19], and CK level was not described in 4 patients [16, 18, 27, 30]. Third, in the pre-cancer immunotherapy era, concomitant inflammatory myopathy or myocarditis usually occurred in thymoma-associated myasthenia gravis [41]; however, none of the patients with PD-1 inhibitor-associated myasthenia gravis-myositis-myocarditis overlap syndrome had thymoma [15••, 37••, 41, 43]. It has been suggested that PD-1 inhibitor-associated myasthenia gravis and thymoma-associated autoimmune disorders may share an underlying pathomechanism [37••]. Elevated striational antibodies were reported in patients with myasthenia gravis-myositis-myocarditis overlap syndrome with and without PD-1 inhibitor exposure [15••, 37••, 41]. In the absence of thymoma, striational antibodies along with creatine kinase may be a

potential useful biomarker of more severe muscle or cardiac involvement in PD-1 inhibitor-treated myasthenia gravis patients. However, striational antibodies have not been reported on a consistent basis in the literature to be certain if this association applies to anti-PD-1 associated myasthenia gravis.

In addition to discontinuation of PD-1 inhibitors, immunomodulatory treatments were required in almost all cases [37••], except one patient with ocular myasthenia who required only pyridostigmine [22] and one with generalized myasthenia who stayed on low-dose prednisone for pre-existing myasthenia gravis and had spontaneous resolution without additional immunomodulatory therapy [20]. Immunomodulatory therapy included either steroid, IVIG, or plasma exchange, alone or in combination. Among 24 patients, whom detailed treatment regimen was available, 8 patients initially received high-dose steroid as a sole immunosuppressant with or without other subsequent immunomodulatory treatments and 5 of them had either progression or no improvement of myasthenic symptoms during steroid therapy [13••, 17, 23, 25, 27, 28, 33, 34]. This is similar to steroid-induced myasthenic exacerbation observed in patients with PD-1 inhibitor-naïve myasthenia gravis [44] . Most PD-1 inhibitor-associated myasthenia gravis patients responded favorably to immunomodulatory therapies, except 10 patients had a fatal outcome, a few of which were cancer-related. The mortality rate in PD-1 inhibitor-associated myasthenia gravis patients is much higher than what was observed in myasthenia gravis patients without exposure to anti-PD-1therapy [45]. Of the 10 deaths, 6 patients had elevated CK [13••, 15••, 24, 26, 28, 33, 37••], 1 had normal CK [19], and the CK was unknown in the other 3 patients [27, 30, 37••]. Although this may suggest that a high CK, suggestive of concomitant inflammatory myopathy or myocarditis, might portend a poorer outcome in PD-1 inhibitor-associated myasthenia gravis, it is difficult to draw a definite conclusion as CK levels were not measured in a significant proportion of patients; CK levels were also elevated in 14 patients who survived myasthenia gravis [20, 25, 29, 32, 34, 35, 37••]. In most cases, patients were not recommenced on anti-PD-1 inhibitor therapy; however, in one case series, two patients with mild myasthenia gravis were subsequently restarted on PD-1 inhibitor therapy without further relapse of myasthenic symptoms, suggesting that this is possible in selected cases [37••]. With regard to the underlying cancer, PD-1 inhibitor-associated myasthenia gravis does not necessarily translate into a good outcome from the malignancy point of view. In the 24 individual case reports reviewed, 3 patients went on to have progression of their underlying malignancy, documented at 4 weeks, 5 weeks, and 5 months post-myasthenia gravis treatment, respectively [13••, 23, 24], while in the series from Suzuki et al., tumor size reduction was only seen in 4/12 patients with nivolumab-associated myasthenia gravis [37••].

To date, there have been no reports of Lambert Eaton myasthenic syndrome (LEMS) in the setting of anti-PD-1 immunotherapy.

Muscle Disorders

Muscle disorders were the second most commonly reported PD-1 inhibitor-associated neuromuscular autoimmunity after myasthenia gravis. However, its estimated frequency was 0.58 to 0.76% among all PD-1 inhibitor-treated patients, which was actually higher than what was reported in myasthenia gravis [12••, 15••]. At least 32 patients (16 nivolumab, 12 pembrolizumab, and 4 combined nivolumab and ipilimumab) were reported with various immune-related adverse events affecting skeletal muscle, including polymyositis ($n = 6$) [25, 35, 36, 46, 47], necrotizing autoimmune myopathy ($n = 3$) [15••, 40], dermatomyositis ($n = 2$) [15••, 48], granulomatous myositis (n = 2) [49], non-specific myopathy (n = 2) [15••], and myositis not otherwise specified ($n = 4$) [37••]. Ten patients were diagnosed with presumptive myositis without undergoing muscle biopsy [26, 32–34, 43, 50–53], one of whom had positive anti-MDA5 antibody [52], or the biopsy findings were inconclusive [43]. A single patient was diagnosed with necrotizing autoimmune myopathy on the basis of a positive serology (anti-SRP antibody) without muscle biopsy [54]. Six patients developed rhabdomyolysis [28, 29, 43, 46, 50, 55], including three patients with coexisting myositis [43, 46, 50]. Myositis was de novo in all, but one patient [51]. Zimmer et al. reported four additional patients with presumptive myositis, but we did not include them in this review due to inadequate clinical information [13••].

Muscle symptoms occurred after a mean and median of 2.4 and 2 treatments of PD-1 inhibitors, respectively (range 1 to 9). Duration between symptom onset and the initiation of anti-PD-1 therapy ranged from 2 to 15 weeks (median, 3 weeks). Proximal or generalized limb weakness are the most common presenting symptoms (60%), followed by ptosis or diplopia (50%), myalgia (45%), dyspnea (35%), dysphagia or dysarthria (25%), fatigue (25%), and head drop (15%). Of interest, half of patients with ocular symptoms were also diagnosed with concomitant myasthenia gravis. Ocular involvement is not a known typical feature of inflammatory myopathy or necrotizing autoimmune myopathy [56]; therefore, ocular symptoms are very unique to PD-1 inhibitor-associated myopathies regardless of the pathological subtypes of myopathies [15••]. Although ptosis and diplopia could be due to coexisting myasthenia gravis in some patients, normal single fiber EMG [35, 48] or abnormal signals of extraocular muscles noted on MRI [15••] in some other patients suggested that the ocular symptoms could be a direct effect of myopathies (orbital myositis) as well. The presence of AChR antibodies in

patient with normal single fiber EMG is of uncertain clinical significance [35]. Concomitant neurologic and non-neurologic immune-related adverse events occurred in 17 of 31 patients with PD-1 inhibitor-associated myopathies, including 14 patients with myasthenia gravis (45%) [15••, 25, 26, 28, 32–35, 37••, 49, 52] and 9 patients with myocarditis (29%) [15••, 25, 36, 37••, 46, 52, 54]. Three patients had myositis, myocarditis and myasthenia gravis [25, 37••, 52]. Myositis, myocarditis, and myasthenia gravis occurred concurrently or during the same hospitalization in all patients. Johnson et al. reported a series of 101 patients with PD-1 inhibitor-associated myocarditis, concurrent myositis and myasthenia gravis occurred in about 25 and 10% of patients, respectively [57]. Only three patients had pre-existing autoimmune disorders prior to PD-1 inhibitor exposure [28, 47, 51], including a patient with statin-induced myopathy with hyperCKemia [51]. Five other patients were on statin at the onset of myopathic symptoms [43, 46, 50].

The CK ranged from 72 to 30,980 U/L (median 2566 and mean 6126). Myositis antibodies were negative in most patients tested. All three patients with biopsy-proven necrotizing autoimmune myopathy were seronegative for anti-HMGCR and anti-SRP antibodies [15••, 40]. Striational antibodies were elevated in some patients, including those with coexisting non-thymomatous myasthenia gravis [15••, 37••, 43]. Myopathological findings in PD-1 inhibitor-associated myopathies are similar to those without PD-1 inhibitor exposure, except for necrotizing autoimmune myopathy that the necrotic fibers appears in a multifocal pattern in PD-1 inhibitor-treated patients compared to a more generalized pattern in PD-1 inhibitor-naive patients [15••, 40]. In inflammatory myopathy, the presence of CD8+ T cells, sometimes more prominent than CD4+ T cells, in an inflammatory exudate in muscle and the increased CD8+/CD4+ T cell ratio in peripheral blood suggest the direct effect of unleashed activated T cells [25, 33, 47, 48]. In granulomatous myositis, macrophages are the most abundant cells in an intramuscular inflammatory exudate, and tumor-infiltrating macrophages have been shown to express PD-1 [49, 58]. Hence, in addition to unleashing T cells, it is possible that PD-1 inhibitors can also affect other immune cells in the tumor microenvironment. Without muscle biopsy, it could be challenging to distinguish between immune-mediated myopathies and rhabdomyolysis.

Patients received a variety of immunomodulatory therapies in addition to discontinuation of PD-1 inhibitors. About 75% of patients responded favorably to the treatment [15••, 25, 26, 32, 34–36, 40, 43, 47–53], but a few subsequently succumbed to cancer, myocarditis, or sepsis, or were transitioned to comfort care measures. High-dose steroid was given as an initial treatment in 16 patients [15••, 25, 33, 34, 36, 40, 43, 46, 49–51, 53, 54], some of whom also subsequently received other immunomodulatory therapies. The remaining patients received high-dose steroid simultaneously with other treatments, mostly IVIG or plasma exchange [15••, 32, 35, 46–49, 52]. Six patients who received initial high-dose steroid monotherapy [15••, 28, 33, 43, 46, 54], two of whom also had PD-1 inhibitor-associated myasthenia gravis, and two patients who received concurrent steroid and other treatments [46, 52] developed deterioration of weakness, especially bulbar or respiratory muscles, or cardiac arrhythmia secondary to myocarditis. In some of these patients, deterioration occurred after a few days of initial improvement or in the setting of lowering CK levels [15••, 28, 32, 36, 43, 52]. A single patient with rhabdomyolysis improved after hydration without initiation of immunomodulators [55]. The detailed treatment regimen was unavailable in patients reported by Suzuki and colleagues [37••].

Peripheral Nerve Disorders

As a group, neuropathies are the most common neuromuscular complications in PD-1 inhibitor-treated patients at an estimated frequency of 1.2–1.6% of all patients undergone anti-PD-1 therapy [12••, 13••]. Acute and chronic neuropathies have been described. These can be focal or diffuse. The former includes oculomotor, abducens, and facial cranial neuropathies [13••]. The latter could be axonal or demyelinating [12••]. Patients with axonal neuropathies often have prior exposure to chemotherapy, making it difficult to attribute such neuropathies directly to anti-PD-1 inhibitor therapy. Mild sensory polyneuropathy and paresthesia can be encountered, which require no specific treatment [59].

Guillain-Barre Syndrome (GBS) GBS is the third most commonly reported PD-1 inhibitor-associated neuromuscular complication and occurred in 0.2to 0.3% of PD-1 inhibitor-treated patients [12••, 13••]. At least eight cases (five nivolumab and three pembrolizumab) have been reported [13••, 60–66]. Unlike anti-PD-1 treatment-associated myasthenia gravis or immune-mediated myopathies, onset is more variable with GBS and can be early or much later in the course of anti-PD-1 treatment, ranging from 2 to 18 doses of PD-1 inhibitors (median 4.5). Duration between symptom onset and the initiation of anti-PD1 therapy ranged from 4 to 68 weeks (median, 12 weeks). GBS may occur a few months after completion of anti-PD-1 therapy [60]. The clinical picture is similar to standard GBS, including electrodiagnostic findings of a demyelinating polyradiculoneuropathy and CSF evidence of albuminocytologic dissociation (CSF protein 73 to 388 mg/dL). The main clue is the temporal relationship to anti-PD-1 inhibitor therapy. Mild CSF pleocytosis has also been reported [60, 64], but not on a consistent enough basis to be reliable as a distinguishing feature. It is nevertheless important to recognize, as the differential would otherwise include leptomeningeal carcinomatosis. MRI may show enhancement of the nerves involved [60]. Antiganglioside antibodies were

rarely encountered, positive in one of eight cases reviewed [65].

Treatment in GBS generally involved IVIG and occasionally plasma exchange. There was one reported case where the patient failed to respond to IVIG but subsequently responded to IV steroids [63], suggesting there may be some differences from PD-1 inhibitor-naïve GBS, where there is typically no steroid responsiveness [67]. This however still appears to be the exception, as in two other cases where steroids were trialed first, the patient either failed to improve [61] or worsened [65]. In both of these cases, subsequent treatment with IVIG led to clinical improvement.

Chronic Inflammatory Demyelinating Polyradiculoneuropathy (CIDP) CIDP is much less commonly reported, with only a small handful of cases. The first case was an 85-year-old woman who developed paresthesia between the sixth and seventh cycle of pembrolizumab treatment, followed by the motor weakness and areflexia over the following 3 months [64]. Despite discontinuation of pembrolizumab and initiation of steroids and plasma exchange, this patient failed to improve. The second case was an 85-year-old woman whose symptom onset was at 2 weeks after the initial dose of nivolumab, starting with paresthesia of the hands and feet and evolving over the ensuing 4 weeks to include weakness of the extremities and dysarthria [68]. The presentation was felt to be consistent with GBS initially and the patient was treated with IVIG with improvement. However, she subsequently developed fluctuating neurological symptoms more suggestive of CIDP and required further treatment with steroids.

In both of cases, ancillary testing were as expected with CIDP. EMG showed evidence of demyelination, including prolonged F wave latencies and motor conduction block. In case two, MRI imaging showed enhancement of the C7 and T1 dorsal roots. Both patients had elevated CSF protein of 74 and 358 mg/dL, respectively, although the second patient also had a mild pleocytosis similar to some of the PD-1 inhibitor-associated GBS cases as mentioned earlier [60, 64].

Motor Polyradiculopathy Another reported variant of anti-PD-1-associated neuropathy is a motor polyradiculopathy [12••, 69]. The presentation in these cases is with asymmetric limb weakness, worsening over weeks to months. In one of these cases, which developed after 23 cycles of pembrolizumab treatment, the patient had serial EMG studies performed at days 10, 36, 86, and 395 after symptom onset [69]. The first EMG performed at day 10 showed normal motor and sensory nerve conduction studies, with fibrillation potentials and reduced recruitment in several examined muscles. The second EMG at day 36 showed reduction in CMAP amplitudes but preserved conduction velocities and absence or minimal prolongation of F waves, preserved sural sensory responses, and needle EMG consisted with severe active denervation. CSF showed albuminocytologic dissociation, with protein of 67 mg/dl. MRI revealed contrast enhancement of ventral lumbosacral nerve roots. The patient worsened despite IVIG but subsequently improved following plasma exchange.

Vasculitic Neuropathy Finally, there have also been a few reports of vasculitic neuropathy. In one case, the patient presented after the initial dose of pembrolizumab with a fairly symmetric but rapidly progressive lower limb weakness [70]. Nerve biopsy in this case showed infiltration of mononuclear cells of small endoneural vessels, suggestive of microvasculitis. In another case, the patient presented after 5 cycles of nivolumab with asymmetric sensory loss and weakness in a manner suggestive of mononeuritis multiplex [12••]. CSF in this patient showed 2 nucleated cells and protein of 71 mg/dL. Sural nerve biopsy showed findings consistent of a necrotizing vasculitis. Both of these patients responded to treatment with steroids monotherapy.

Conclusions

Although neuromuscular complications are uncommon among patients undergoing anti-PD-1 therapy, they have certain characteristic features that set them apart from their PD-1 inhibitor-naïve counterparts, especially in those patients with myasthenia gravis and immune-mediated myopathies. With potentially fatal outcome among these patients, early recognition, prompt treatment, and surveilling for other concomitant immune-related adverse events, especially myocarditis, are of the utmost importance. Oculobulbar and/or respiratory muscle weakness are the most diagnostically challenging symptoms in PD-1 inhibitor-treated patients as this could be from cranial neuropathy, Guillain-Barre syndrome, myasthenia gravis, immune-mediated myopathies, or a combination of any of these. Myalgia and fatigue, albeit non-specific, could be manifestations of immune-mediated myopathies. Discontinuation of PD-1 inhibitors and initiation of immunomodulatory treatments generally lead to a favorable outcome. High-dose steroids monotherapy is commonly used in patients with PD-1 inhibitor-naïve inflammatory myopathies or PD-1 inhibitor-associated non-neuromuscular autoimmune disorders, but this should be avoided in patients with PD-1 inhibitor-associated myasthenia gravis, immune-mediated myopathies, and Guillain-Barre syndrome, given it can potentially cause deterioration of symptoms in some patients. Close follow-up during the initial phase of treatment is also important as these patients could deteriorate after the initial improvement, part of which could be a result of concurrent myocarditis. A long-term prospective study is required to determine the rationale for continuation of an immunomodulatory therapy in patients with PD-1 inhibitor-associated neuromuscular complications.

Compliance with Ethical Standards

Conflict of Interest Justin C. Kao, Adipong Brickshawana, and Teerin Liewluck declare no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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