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Review

Clinical spectrum of neuromuscular complications after immune checkpoint inhibition

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Abstract

Cancer immunotherapy has transformed the field of oncology and enabled more effective management of previously refractory neoplasms by activation of the immune response. Upregulation of the immune response may also trigger autoimmune adverse events, including neuromuscular complications. We performed a systematic review of autoimmune neuromuscular complications following immune checkpoint blockade. We searched PubMed database and identified 81 cases described, including 30 cases of myasthenia gravis (MG), 29 cases of neuropathy and 22 cases of myopathy. Most patients (89%) developed neuromuscular complications within 3 months from starting immune checkpoint blockade and 40% of all patients had elevated serum CK>1000 IU/L (typical normal <200). Guillain-Barre syndrome variants and overlaps of MG with myositis and/or myocarditis also occurred. One quarter of myasthenia patients presented with exacerbations of previously diagnosed myasthenia gravis, while neuropathy and myopathy typically presented with a new onset. Most patients improved with immunomodulatory treatment, but neuromuscular complications were sometimes refractory and associated with high mortality of 26% from cancer recurrence, comorbidities, or treatment complications. Poor outcomes were more common with exacerbations of pre-existing myasthenia gravis and myocarditis overlap. Future prospective studies are needed to elucidate mechanisms and risk factors for autoimmune adverse events following immune checkpoint blockade.

Keywords: Immune checkpoint inhibitors; Neuromuscular; Myasthenia gravis; Neuropathy; Myopathy.

1. Introduction

Cancer immunotherapy continues to have a great impact on clinical practice in oncology as it enabled effective treatment of previously refractory neoplasms by activation of the immune response. Blockade of inhibitory immune checkpoint molecules shifts the balance toward antitumor immunity which allows more effective control of tumor growth and improves clinical outcomes [1]. Immune checkpoint molecules maintain immunologic homeostasis and play an important role in *T*-cell maturation and regulation of peripheral tolerance to prevent autoimmune responses. The most well-known immune checkpoint molecules include cytotoxic *T*-lymphocyte antigen-4 (CTLA-4) and programmed cell death protein - 1 (PD-1) and its ligand PD-ligand 1 (PD-L1). Mechanisms of immunoregulation by CTLA4 and PD-1/PD-L1 are not identical, as CTLA4 mediates early phase *T*-cell activation, while PD1/PD-L1 pathways regulate the late stages [2]. Additionally, CTLA4 is primarily expressed in lymphoid tissue, while PD-1/PD-L1 are more expressed in various types of peripheral tissue [2]. Early use of cancer immunotherapy focused on melanoma, but it is now more widely used in other types of cancer, including first-line therapy of non-small lung cancer. Blockade of CTLA4 and/or PD-1/PD-L1 pathways by immune checkpoint inhibitors (ICI) and upregulation of the immune system may in turn trigger immune-related adverse events (irAE) with worsening of preexisting or new onset of

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various autoimmune disorders, including a wide array of neurologic complications [3,4].

Neurologic complications of varying severity, involving both central and peripheral nervous systems, have been reported in up to 6% of treated patients [5,6]. Overall, neuromuscular complications following ICI have been relatively rare compared to other autoimmune adverse events, but the rate is still much higher than in the general population [7,8]. While most patients present with the new onset of a neurologic autoimmune disorder, up to 27% of ICI-associated MG cases may be related to exacerbations of pre-existing or subclinical MG [9]. Other types of neuromuscular complications, including immune-mediated neuropathies and myopathies, typically present as new onset conditions.

In this review, we report the clinical spectrum of neuromuscular complications following the use of immune checkpoint inhibitors.

2. Methods and overview of neuromuscular complications

We searched the literature through Pubmed/Medline for relevant key words including "immune checkpoint", "immune checkpoint inhibitor", and individual ICIs (ipilimumab, tremelimumab, nivolumab, pembrolizumab, durvalumab, atelizumab, avelumab), combined with "myasthenia gravis", "neuropathy", "myopathy", "myositis" or "neuromuscular". The search was conducted in February 2018. We have identified and screened 180 unique publications (eFigure in the supplement). We extracted cases from both series and individual case reports (evidence level 4 and 5). We selected articles with sufficient clinical information for confirmation of neuromuscular diagnosis and data for analysis, otherwise they were excluded. If it was not possible to separate individual case from series data, we did not utilize those cases for analysis but mention the series in the discussion when appropriate.

We included 61 publications including case reports and series from peer-reviewed journals, and we also included 3 cases from our series previously presented as a poster and an abstract, describing neuromuscular adverse events following ICI therapy involving 81 patients of which there were 37% women with a mean age of 65.4 years (range 27–86) (Table 1). Among those cases, there were 30 patients with primary neuromuscular diagnosis of acquired MG; 29 patients had neuropathy, and 22 had myopathy. The ICI used included ipilimumab (n=33), pembrolizumab (n=31), nivolumab (n=30), tremelimumab (n=2) and durvalumab (n=2). Sixteen patients were treated with a combination of ICI prior to the onset of irAEs (20%). Neuromuscular complications presented within 3 months from starting ICI in 89% of patients (72/81) and within the first two cycles in 56% (45/81).

Primary neoplasms included melanoma (n=56, 69%), non-small cell lung carcinoma (n=9) and small cell lung carcinoma (n=2), renal cell carcinoma (n=4), and bladder carcinoma (n=2). Thymoma, non-Hodgkin lymphoma, glioblastoma, Merkel cell carcinoma, gastroesophageal carcinoma, colorectal carcinoma, prostate carcinoma, and uterine carcinosarcoma occurred in one each. There were 21 cases with fatal outcomes (26% mortality) attributed to cancer progression, comorbidities or treatment complications. Spontaneous resolution without immunomodulatory treatment of neuromuscular symptoms was reported in 3 patients (4%), and 1 patient improved following thyroid supplementation (1%). Most patients (89%) had new onset of immune-mediated neuromuscular complications, except for 8 patients with MG and 1 patient with pre-existing myositis.

2.1. Myasthenia gravis

There were 30 patients with new onset or exacerbations of MG, most often with a generalized presentation (93%). Seventy percent had acetylcholine receptor (AChR) antibody-seropositive MG (n=21), with 2 previously AChR-seropositive patients converting to AChR-seronegative after ICI. So far, there has been no reported case of muscle specific kinase (MuSK)-positive MG following ICI.

Anti-MuSK antibody titers were negative when checked (n=12), and there were four patients with elevated anti-striated muscle antibodies [including two with MG/hyperCK (creatine kinase)emia overlap]. There was a frequent co-occurrence of MG with muscle disorders (n=14), manifesting as elevated muscle enzymes, myositis and myocarditis. Fourteen patients had MG with hyperCKemia and CK > 1000 IU/L (47%; CK range 1106–10,286 IU/L, nl usually <200). There were 2 patients with biopsy-proven inflammatory myopathy, and one with rhabdomyolysis [10–12]. Combination of MG and myocarditis was found in three patients treated with the PD-1 inhibitor nivolumab [10,13,14]. There were 2 patients with overlap syndrome of myasthenia, neuropathy and myopathy [15,16].

Symptom severity varied significantly, with 12 refractory fatal cases (40% mortality) and two patients with generalized AChR-seropositive myasthenia exhibiting a self-limited clinical course with complete resolution of neuromuscular symptoms without immunosuppressive therapy (7%). In addition, there were 8 patients (27%) with exacerbations of pre-existing known MG with a reported mortality of 63%. All reported cases of ICI-related MG presented within 3 months of starting ICI treatment, and 50% improved with immunomodulatory treatment.

2.2. Peripheral neuropathies and radiculopathies

There were 29 patients with ICI-associated new onset of neuropathy of various types, including Guillain-Barre syndrome variants (n=13), chronic inflammatory demyelinating polyneuropathy (CIDP) (n=4), sensorimotor polyneuropathy (n=3), polyradiculopathy (n=5), neuromyopathy, mononeuritis multiplex, cranial polyneuropathy and phrenic nerve palsy (n=1 each). Laboratory testing showed elevated cerebrospinal fluid (CSF) protein in the 20 of 22 cases in which it was checked (range 27–749 g/dl; 13/22 with protein >100 g/dl, normal 15–45 g/dl). Pleocytosis in the CSF (>10 WBC/mm^3)

Table 1
Neuromuscular complications of immune checkpoint inhibitors [5,9–13,21,23,24,26,28,29,31,33–75].

	Myasthenia gravis	Neuropathy	Myopathy
N	30	29	22
Age	age 45–85 years (mean 70.6)	age 31–85 years (mean 59.6)	age 44–86 years (mean 65.9)
Gender	40% women (*n*=12)	31% women (*n*=9)	41% women (*n*=9)
Cancer	Melanoma (15); Non-small cell lung carcinoma (6); Small cell lung carcinoma (2); Renal cell carcinoma (2); Uterine carcinosarcoma (1), Bladder carcinoma (1); Colorectal carcinoma (1); Thymoma (1); Glioblastoma (1)	Melanoma (24); Renal cell carcinoma (2); Prostate carcinoma (1); Non-small cell lung carcinoma (1); Merkel cell carcinoma (1)	Melanoma (17); Non-small cell lung carcinoma (2); Gastro-esophageal adenocarcinoma (1); Lymphoma (1); Bladder carcinoma (1)
Immune checkpoint inhibitor	IPI – 3, NIV – 13, PEM – 11, NIV + IPI – 3	IPI – 11, NIV – 4, PEM – 6, IPI + NIV – 4, IPI + PEM – 3, IPI+PEM+NIV – 1	IPI – 5, NIV – 3, PEM – 9, IPI + NIV – 2 TRE + DUR – 2, IPI + PEM – 1
Phenotype	Generalized – 28, Ocular – 2	GBS – 13, CIDP – 4, Polyradiculopathy – 5, Polyneuropathy – 3, Mononeuritis multiplex – 1, Phrenic palsy – 1, Cranial polyneuropathy – 1, Neuromyopathy – 1	Necrotizing myopathy – 4, Inflammatory myopathy/ myositis – 6, Nonspecific myopathy – 9, Orbital myositis – 2, Hypothyroid myopathy – 1
Other clinical features	CK > 1000 IU/L – 14, Rhabdomyolysis – 1, Myocarditis – 3	Rhabdomyolysis – 1, Optic neuritis – 1, Spinal root enhancement (MRI) – 8	Orbital myositis – 3 (1 overlap), Myocarditis – 6, Rhabdomyolysis – 3,
Outcome	Improved with treatment – 15; Died – 12; Refractory – 1; Spontaneous resolution – 2	Improved with treatment – 23; Died – 3; Refractory – 3	Improved with treatment – 12; Died – 6; Refractory – 3; Spontaneous resolution – 1

Abbreviations: IPI – ipilimumab; TRE – tremelimumab; NIV – nivolumab; PEM – pembrolizumab; DUR– durvalumab

was reported in 8/15 patients (range 0–158 WBC/mm^3; normal <5). Nerve biopsies were obtained in two patients showing segmental demyelination (clinical diagnosis of Guillain-Barre syndrome) and perivascular inflammation (clinical diagnosis of polyneuropathy), and there was one patient with a normal nerve biopsy and predominant clinical features of myasthenia gravis [17–19]. Two patients had elevated titers of anti-nerve antibodies (N6S and heparin-sulfate; GD-1a and GM3 antibodies) [20,21]. Spinal magnetic resonance imaging (MRI) showed spinal root enhancement in 8 patients (28%) with Guillain-Barre syndrome and radiculopathies, typically with high CSF protein levels (5/8 with CSF protein >200 mg/dl). There were no other triggers reported that are known to precipitate GBS aside from the ICI. There were two neuropathy patients with concurrent rhabdomyolysis and optic neuritis (one each). Three patients had hyperCKemia with CK>1000 IU/L, including one with rhabdomyolysis.

Most patients developed neuropathy within 3 months from starting ICI (74%), but 2 patients (7%) had late onset of irAEs beyond 9 months from the first ICI treatment cycle. Most patients improved after withdrawal of ICIs and immunomodulatory treatment (79%), and there were 3 fatal cases (10%).

2.3. Myopathy

There were 21 patients with primary myopathies and one with hypothyroid myopathy, in addition to 14 patients with MG and muscle complications, and three patients with neuropathy who had muscle-related complications (including hyperCKemia, rhabdomyolysis, or biopsy-proven myopathy). Overall, any kind of muscle complication was reported in 40/81 patients (49%). Muscle biopsies were obtained in 20 patients, including 3 patients with predominant myasthenia and 4 patients with predominant neuropathy. There were 10 patients with new onset of biopsy-proven autoimmune myopathies (including reports of necrotizing autoimmune myopathy, polymyositis and dermatomyositis), and one patient had an exacerbation of pre-existing inflammatory myopathy (Table 1). The histopathologic findings of muscle biopsies varied from nonspecific myopathy to inflammatory myopathies resembling dermatomyositis and necrotizing autoimmune myopathy [22,23]. The lack of inflammatory changes on some muscle biopsies was potentially attributable to sampling limitations with patchy muscle inflammation, but other non-inflammatory myopathy mechanisms cannot be entirely excluded. Myopathy was complicated by myocarditis in

6 patients (27%), and one third of patients with necrotizing and inflammatory myopathies had ocular symptoms (ptosis, diplopia). There were also three additional patients with orbital myositis [22,24]. One patient had hypothyroid myopathy with rhabdomyolysis [25]. Muscle tenderness and myalgias were reported in 40% of patients with myopathies.

Serum CK was elevated in 36/55 of patients (65%; range 72–30,980 IU/L; 31 with CK > 1000 IU/L and 14 with CK > 5000, normal usually <200). There were 12 patients with high transaminases in the setting of high CK, and 4 other patients with weakness and high transaminases whereas CK was not reported. There were two patients with elevated myositis antibodies (first – PM-Scl; second – SRP and PL-12B) [22,26]. Anti-striated muscle antibodies were elevated in four patients with primary myopathy and two patients with MG/hyperCKemia overlap.

2.4. Treatment of ICI-related neuromuscular complications

Treatment of neuromuscular irAEs included corticosteroid monotherapy (n=27), IVIG (n=3) or plasma exchange alone (n=1), corticosteroids with either IVIG (n=16) or plasma exchange (n=11), corticosteroids and mycophenolate (n=1), corticosteroids and infliximab (n=1), and combinations of: (a) corticosteroids, IVIG and plasma exchange (n=9), (b) corticosteroids, IVIG and mycophenolate (n=1), (c) corticosteroids, tacrolimus and infliximab (n=2), (d) corticosteroids, infliximab, IVIG and plasma exchange (n=1), (e) corticosteroids, IVIG, plasma exchange and rituximab (n=1), (f) corticosteroids, IVIG, plasma exchange, mycophenolate and rituximab (n=1), and (g) plasma exchange, IVIG and rituximab (n=1). Sixty-three percent of patients improved with treatment; 9% did not improve, and 23% died. Four patients (5%) improved without immunomodulation or immunosuppressive treatment, including one patient who improved with thyroid supplementation. Treatment with ICI was discontinued in most patients, but some have opted to continue ICI, usually due to refractoriness of cancer. Rechallenge with ICI had mixed outcomes with some patients experiencing recurrent irAEs and others tolerating treatment without complications [23,27,28].

3. Discussion

3.1. Incidence of neurologic and neuromuscular complications

Reports of neurologic complications of ICI have been increasing in parallel to the more frequent use of these agents in different types of cancer. Data reported in this study cannot be used to calculate incidence or prevalence of various neuromuscular disorders in patients treated with ICI. Additionally, the reporting format was not standardized, and some of the test results were reported only in selected groups of patients (e.g., serum CK was reported for 68% of patients, and striated muscle antibodies were checked only in 12% of patients). Previous studies showed a greater risk of neurologic complications 12% with combined CTLA4 and PD1/PD-L1 inhibitors, followed by 6.1% with PD1/PD-L1 blockers, and 2.8% with CTLA4 inhibitors alone [6]. Most patients in these series were treated with PD-1/PD-L1 inhibitors alone (57%), followed by CTLA-4 inhibitors (23%) and combination therapy (20%).

The onset of neuromuscular irAEs typically occurred within 3 months from starting ICI, similarly as with other ICI-related irAEs. Delayed occurrence beyond the first 3 months was seen only in 11% of patients with ICI-related neuropathy and myopathy, mostly with the use of PD-1/PD-L1 inhibitors alone or in combination with CTLA4 inhibition. Although neuromuscular complications of ICI are rare, they may still be 30 to 100-fold more common than in the general population [8,22]. Although the reported incidence of ICI-associated myopathies is exceedingly low at 0.7%, some were classified as inflammatory myopathies (0.45%), which would represent more than 30-fold increased risk of inflammatory myopathies when compared to general population [22,29]. Reported cases in these series show a high mortality of 23% that was sometimes not directly related to neuromuscular complications illustrating the severity of comorbidities in this population. It is also difficult to estimate mortality associated with irAEs in this population of patients with typically refractory cancer and multiple comorbidities as many will succumb to cancer. Lower prevalence of post-ICI neuromuscular irAEs in women (38%) is probably related to greater risk of advanced melanoma in men as most of patients in these series were treated for melanoma. Notable is a high prevalence of muscle complications in 49% of patients, manifested by high serum CK, myopathy, rhabdomyolysis or myocarditis, and including various overlap syndromes.

3.2. Overlap syndromes

While the phenotype of ICI neurologic complications may resemble classic presentations, there were several patients with typically rare overlap syndromes including MG with myocarditis or polymyositis that are only rarely seen in the general population [8,10,30,31]. There were also two patients with triad of AChR-seropositive myasthenia, hyperCKemia (CK > 1000 IU/L) and neuropathy [15,16]. The post-ICI combination of MG-myocarditis was most common after use of PD-1 inhibitors, but both MG and myocarditis alone have been previously described separately with CTLA4 blockade as well [8,32,33]. Differences in mechanisms and pathways of inhibition of CTLA4 and PD-1/PD-L1 may explain some of phenotype variations. The presence of other concurrent autoimmune disorders demonstrates multisystemic immune activation with cancer immunotherapy (e.g., hypophysitis, colitis) [4,34]. This phenomenon was illustrated by a case of severe thyroiditis following the use of ipilimumab and pembrolizumab, which then precipitated rhabdomyolysis [25]. Additionally, while autoimmune hepatitis may follow ICI, high transaminases may be also caused by muscle breakdown and should not be mistaken as pathognomonic evidence of primary liver injury [35]. High prevalence of hyperCKemia is

probably underestimated in these series as there were few patients with weakness and high transaminases whereas serum CK was not reported. Likewise, the prevalence of myocarditis may have been underestimated as some patients who were not diagnosed with myocarditis developed arrhythmias and myocardial infarctions [36,37]. In patients with myopathies there was an unusually high prevalence of ocular symptoms which are typically rare with most myopathies. Imaging studies showed extraocular muscle thickening and enhancement in some patients with diplopia, suggestive of orbital myositis, but diplopia might have also been suggestive of myasthenia/myositis overlap.

3.3. Mechanisms and pathways of post-ICI neuromuscular complications

Immunologic mechanisms of post-ICI neuromuscular complications are not well understood and may be related to induction of autoreactive *T*-cells, autoantibodies and altered cytokine patterns [4]. Interestingly, there was a noticeable difference in tumor profile with different neuromuscular irAEs whereas 83% of patients with neuropathies and 77% of patients with myopathies had underlying melanoma, compared to only 50% of patients with myasthenia. This may be potentially attributable to cross-reactivity of peripheral nerve and muscle with melanoma antigens targeted by autoreactive *T*-cells and autoantibodies. Surprisingly, two MG patients treated with PD-1 inhibitors reportedly became AChR-seronegative during post-ICI exacerbations, perhaps similar to epitopal shifting as previously reported after CTLA-4 blockade in a murine model of MG [38]. Pre-existing autoimmune conditions may increase the risk of post-ICI irAE, and such patients were typically excluded from clinical studies investigating ICI in treatment of cancer. However, more than one quarter of MG cases after ICI were exacerbations of pre-existing myasthenia gravis, and these were often associated with greater morbidity than new onset MG. Blockade of immune checkpoint molecules may also unmask subclinical autoimmune disorders with two patients shown to have elevated titers of autoimmune antibodies prior to onset of ICI treatment and clinical symptoms [11,39]. In addition to AChR-seropositive MG patients, there were patients with elevated titers of anti-striated muscle antibodies (n=8), anti-nerve antibodies (n=2) and myositis antibodies (n=2) showing the complexity of immune activation following immune checkpoint blockade. There was not a single antibody subtype or profile associated with several post-ICI neuropathy or myopathy cases. The prevalence of individual antibodies could not be established based on available case reports and case series as relatively few patients were checked for most of individual antibody titers. Interestingly, even though CTLA4 blockade has been used to elicit a paraneoplastic-like response in an animal model [40], so far none of the reported ICI-related irAEs demonstrated elevated titers of paraneoplastic autoantibodies or typical paraneoplastic neuromuscular syndromes of sensory neuronopathy or Lambert-Eaton myasthenic syndrome.

3.4. Surveillance

At this time, it remains unclear whether early diagnosis and intervention can improve outcomes in most patients with post-ICI neuromuscular irAEs, but the severity of comorbidities dictates a low threshold for investigations, especially in patients with a prior diagnosis of MG. Additionally, the presence of new onset of myalgia, weakness or fatigue should prompt consideration of possible myositis, rhabdomyolysis and myocarditis, or new onset of neuropathies or neuromuscular junction disorders. Elevated transaminases in the absence of other signs of liver injury may be another indication of muscle breakdown in patients with weakness or myalgias. Depending on clinical findings, additional testing may include serum CK, AChR antibodies, troponin and CK-MB, while CSF evaluation may be required when investigating possible Guillain-Barre syndrome. Additional serologic, electrodiagnostic and imaging testing is needed depending on individual case features. Nevertheless, while evaluating for possible irAEs, we should also consider whether some symptoms may be related to progression of cancer or comorbidities which may mimic or coexist with neuromuscular irAEs [41].

3.5. Treatment of post-ICI neuromuscular complications

Treatment of irAEs is typically based on stopping the offending agent and starting corticosteroids, which are often combined with IVIG or plasma exchange [34,42]. The goal is to strike a balance between effective treatment of cancer and management of irAEs. Progression or recurrence of cancer or refractory autoimmune complications may be associated with substantial morbidity and mortality. Upon the onset of severe neurologic autoimmune adverse events, cancer immunotherapy is usually discontinued and it remains unclear as to how and when it is safe to restart ICIs since some patients experienced irAEs recurrence upon rechallenge [23]. The use of cytotoxic immunosuppressants is generally avoided. In exception, the use of mycophenolate mofetil has been recommended with grade 3–4 hepatitis and pneumonitis, while infliximab may be used for colitis [42]. At this time, it still remains uncertain and of great concern whether treatment of autoimmune adverse events may potentially undermine the efficacy of immunotherapy in cancer treatment. Fortunately, most of the patients with neuromuscular irAEs following ICI improved upon discontinuation of cancer immunotherapy and commencing immunomodulatory therapy suggesting that the autoimmune switch may be temporary.

Adverse outcomes were more often reported in patients with pre-existing MG suggesting that a more active approach with close surveillance and early treatment may be needed in that particular group. Likewise, myocarditis was also associated with poor prognosis as only one-third of patients responded to therapy, probably warranting a more aggressive approach with earlier treatment of patients with overlap syndromes involving myocarditis. At this time, it is too early to determine the long-term consequences of ICI on autoimmunity and outcomes in chronic disorders like MG and CIDP.

4. Conclusions

This review is inherently limited by its design (aggregate post-hoc review of non-standardized case reports and series), but the reviewed data provides important insights into neuromuscular complications associated with ICI. Emerging patterns show high prevalence of muscle-related complications, frequent overlap syndromes of MG and myositis and/or myocarditis, and variants of inflammatory neuropathies. Most patients develop neuromuscular irAEs early in the course and respond to treatment, but complex comorbidities and overlaps of myositis-myocarditis and MG-myocarditis may be associated with unfavorable outcomes. Future systematic studies are needed to investigate mechanisms and risk factors for autoimmune adverse events following cancer immunotherapy (including neuromuscular disorders) and to optimize management and long-term outcomes.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.nmd.2018.11.012.

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