REVIEW ARTICLE

Myasthenia Gravis in Patients Treated With Immune Checkpoint Inhibitors

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ABSTRACT

Background: Immune checkpoint inhibitors (ICIs) have improved outcomes significantly for patients across multiple tumor types, and now are being used in combination with other therapies and in earlier settings where treatment intent is curative. Immune-related adverse events occur commonly and there are clear guidelines regarding management. Neurological toxicities such as myasthenia gravis (MG) with or without myositis are rare but are associated with high morbidity and mortality.

Methods: This single-centre study presents a series of patients treated with ICIs who subsequently developed immune-related MG. Presenting symptoms, treatments and outcomes were abstracted from retrospective chart review.

Results: We identified 16 patients (9 thoracic malignancies, 7 other tumor sites) who were diagnosed with MG after one or more cycles of ICI. Eleven had overlapping myositis. The median time from the first ICI treatment to the onset of symptoms was 49 days (range 17–361). All patients received steroids (prednisone 1–2 mg/kg); six required other immunosuppressive agents, and five underwent plasma exchange. Only two patients had complete resolution, eight improved with residual symptoms, two experienced initial improvement followed by deterioration, and four worsened despite treatment. Six patients died as a result of myasthenia-related complications (38%), three from progressive cancer (19%) and seven remain alive at the time of review (44%).

Conclusion: ICI-related MG is a rare and potentially fatal adverse event. Diagnosis and management remain a challenge, especially with negative serological markers and in the presence of overlapping syndromes with high mortality rates. Prompt recognition and multimodality treatment are key. Clinicians should have a low threshold for diagnosis and early management.

Keywords: Myasthenia gravis; Immune checkpoint inhibitors; Immune-related neurotoxicity; Myositis-myocarditis overlap

Introduction

Immune checkpoint inhibitors (ICIs) have become standard of care in the treatment of several solid organ malignancies, including both SCLC and NSCLC cancers and malignant melanoma, where they have improved

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patient survival and long-term outcomes significantly. In the advanced setting, ICI has improved melanoma 5-year survival to 52% with median survival of greater than 60 months, and NSCLC 5-year survival to 19.4% versus 11.3%, with median survival of 21.8 months versus 12.1 months.[1,2] Survival benefits are durable in resected melanoma with ongoing benefit of almost 10% difference at 7 years follow-up with adjuvant ipilimumab and 17 % difference at 5-years with adjuvant pembrolizumab.[3,4] In both the adjuvant and neo-adjuvant setting in NSCLC, ICI use also has resulted in a significant survival advantage.[5,6] Due to their unique mechanism of action, ICIs can cause several immune-related toxicities, most commonly affecting the gastrointestinal tract, skin, liver and endocrine glands.[7] Rarely, neurologic adverse effects are seen with an estimate of 1% to 5% of patients, but may be as high 12% with combination ICIs, particularly CTLA4 inhibitors which are used more frequently in melanoma.[7–10] Myasthenia gravis (MG), encephalitis and peripheral neuropathy are among the most common, and frequently are associated with myositis and less frequently myocarditis.[8–10]

MG post-immunotherapy is associated with high morbidity and mortality.[9–12] It can occur as an exacerbation of pre-existing MG or de novo. The clinical picture typically is characterized by progressive weakness affecting the extra-ocular, bulbar and limb muscles, and when diaphragmatic muscles are involved, may progress to respiratory failure in 20% to 50% of reported cases.[9–13] MG is commonly seen in association with immune-mediated myositis in approximately 30% of cases or myocarditis in 8% of the cases, and is referred to as MG-myositis or MG-myocarditis overlap syndromes respectively.[9–12,14] This overlap syndrome is especially challenging and life-threatening.[9–14]

We present here our single-centre experience from the University Health Network and Princess Margaret Cancer Centre of patients with malignancies who developed MG in the setting of treatment with ICIs.

Methods

This was a single-centre retrospective analysis. Patients who had been treated with at least one cycle of a checkpoint inhibitor and subsequently were diagnosed with myasthenia were identified by oncology and neurology physicians involved in their care. Retrospective chart review was performed to collect relevant clinical information, including baseline patient demographics, tumour histology, systemic therapy received including chemotherapy, PD-1, PDL-1 or CTLA-4 inhibitor therapy, confirmatory diagnostic tests for myasthenia, treatment and outcomes. The study was approved by the Research Ethics Board of the Princess Margaret Cancer Centre. Written informed consent was waived as this was a retrospective chart review study.

Diagnosis of MG was considered definite if acetylcholine receptor (AChR) antibodies or muscle-specific tyrosine kinase antibodies were present and/or the results of electromyography (EMG) studies (including repetitive nerve stimulation and single fibre EMG) were consistent with the diagnosis. The diagnosis was considered highly probable if the diagnosis of MG was based on a high clinical suspicion of the treating neurologist. Diagnosis of myositis was considered when there was also elevation of creatine phosphokinase or suggested by EMG studies.

Results

Patient Demographics

Between July, 2017 and April, 2024, 16 patients were identified, nine with thoracic malignancies, and seven from other sites (Table 1). Eleven patients also had myositis/ myocarditis syndrome; Six of those had concurrent ICI-induced hepatitis. Only one patient with melanoma had a pre-existing diagnosis of MG before starting immunotherapy. At the time of diagnosis of MG, 50% were receiving PD-1 or PDL-1 inhibitors alone; three patients received a combination of PD-1 or PDL-1 with CTLA4 inhibitors; two received PD1 or PD-L1 inhibitors with tyrosine kinase inhibitors, one received a PD1 inhibitor with a TIM3 inhibitor; only two received PD1 or PD-L1 in combination with chemotherapy. The median time from the first ICI treatment to the onset of symptoms was 49 days (range 17-361). The median number of cycles of ICI received prior to diagnosis was 2.5 cycles (range 1-12). The most common presentations were bulbar, and ocular involvement at 88% and 72%, respectively; Four patients developed respiratory failure and required ventilation support. Among 11 of 16 patients tested, positive AChR antibodies were seen in only one case while 10 were negative. Electromyography (EMG) was performed in only 11 patients; nine tests were diagnostic of MG (56%). Six cases of MG were diagnosed as highly probable as the diagnosis was clinical, and based on high clinical suspicion with either negative or unevaluable antibodies or EMG.

Treatment and outcomes

All patients received steroids at a dose of oral prednisone 1-2mg/kg or equivalent; five patients received pulse steroid of 1 gram solumedrol intravenously (Table 2). Four patients received steroid only. Only three patients responded to steroids alone, and one died before other treatments could be given. Eleven patients received intravenous immunoglobulin (IVIG); five patients underwent plasma exchange (PLEX). Additional immune-

Table 1. Clinical Characteristics, Diagnostic Findings

Baseline Demographics	Myositis/Myocarditis (n = 11)	Hepatitis (n = 6)	All (N = 16)
Median age in y, (range)	73 (57-81)	73 (57-81)	71 (57-86)
Sex			
Male	6	4	7
Female	5	2	9
Malignancy			
NSCLC	6	3	5
SCLC	2	1	2
Mesothelioma	2	1	2
Melanoma	0	0	3
Other[a]	1	1	4
Immunotherapy treatment			
PD1/PDL1 alone	5	2	8
PD1/PDL1+CTLA4	2	1	3
PD1/PDL1+chemotherapy	2	1	2
PD1/PDL1 + others[b]	2	2	3
Number of immunotherapy cycles			
1	3	3	3
2	4	3	5
≥3	4	0	8
Time from IO to symptoms (d)	47 (17-97)	26 (17-49)	49 (17-361)
Clinical presentation			
Bulbar	9	5	14
Ocular	9	6	13
Limb weakness	2	2	6
Dyspnea	4	2	4
Diagnosis			
Clinical only	5	3	6
Antibodies	1 positive 8 negative 2 unknown	1 positive 5 negatives	1 positive 10 negatives 5 unknown
EMG	5 positive 2 negative 4 not performed	2 positive EMG 1 negative 3 not performed	9 positive 2 negative 5 not performed

[a]Head and neck, chordoma, thymoma, endometrium, one case each.
[b]TIM3 antibody, cabozantinib; niraparib, one patient each.
EMG, electromyography; IO, immunotherapy.

suppressants used in six patients included mycophenolate mofetil in three patients and infliximab, rituximab, and abatacept as part of a clinical trial for ICI-myositis in one patient each.

Only two patients had complete clinical resolution and were able to discontinue steroid therapy; eight patients improved with residual symptoms and were able to taper steroids; four continued to worsen despite treatment. Six patients died as a result of myasthenia-related complications (38%), three patients died from progressive cancer (19%) and seven patients are still alive at the time of review (44%). Among the 11 patients with myositis/myocarditis overlap syndrome, five were alive at the time of the review while only 3 were alive among those with concurrent ICI-hepatitis.

With respect to best tumor response and cancer-specific survival outcomes, one patient achieved complete remission, seven partial remission; four stable disease while the remaining four experienced progressive disease.

Discussion

ICIs now are used routinely in patients across many types of malignancies. PD-1/PD-L1 inhibitors are the most commonly used, either as monotherapy or in combination with other agents in the advanced, and more recently the neoadjuvant and adjuvant potentially curative settings.[15] ICI-related neurologic complications including MG are rare and often difficult to recognize at presentation as symptoms are non-specific such as generalized weakness and fatigue. These often are attributed incorrectly to the advanced cancer, which may lead to delayed diagnosis and initiation of treatment.[9,10,12] Among our patients, six (38%) gave a history of increasing weakness or fatigue before more specific neurologic symptoms and signs emerged.

Table 2. Treatment and outcomes

Treatment & Outcomes	Myositis/Myocarditis (n = 11)	Hepatitis (n = 6)[a]	All (N = 16)
Treatment			
Steroids	11	6	16
Acetylcholine inhibitors	6	3	10
Intravenous immune globulin	7	4	11
Plasma exchange	2	1	5
Additional immunosuppressant			
Mycophenolate	1	1	3
Rituximab	0	0	1
Infliximab	1	1	1
Abatacept[b]	1	1	1
Ventilation support	4	2	4
Myasthenia Gravis outcomes			
Complete resolution	1	1	2
Improved	6	3	8
Improved with subsequent relapse	1	1	2
Deteriorated	3	1	4
Death from myasthenia	4	2	6
Tumor outcomes			
CR	0	0	1
PR	5	2	7
SD	3	3	4
PD	3	1	4
Median survival in mo from diagnosis of myasthenia (range)	4.3 (0.9-15.5)	2.3 (0.9-15.5)	6.3 (0.9-18.5)

[a]Six of the patients with overlapping myositis/myocarditis syndrome had concurrent ICI-hepatitis.
[b]Abatacept was given as part of a trial for immune-induced myositis.
CR, complete response; ICI, immune checkpoint inhibitor; PD, progressive disease; PR, partial response; SD, stable disease.

Because of the early uptake of ICI treatment in thoracic malignancies and malignant melanoma, more than half of our patients had thoracic cancers (56%). Eleven patients (69%) had received either PD-1/PD-L1 inhibitors alone or in combination with CTLA4 in the melanoma cases. The median onset of symptoms in our series was 7 weeks, which is slightly longer than the 4 weeks (range 6 days – 16 weeks) reported in the literature.[9–13]

Specific symptoms which lead to a diagnosis may include ptosis, diplopia, dysphagia, dysarthria and dyspnea.[9–11,13] Indeed, 14 of our 16 patients had bulbar and ocular symptoms at presentation. Symptoms may progress rapidly with decompensation to a myasthenic crisis requiring respiratory support and mechanical ventilation in 40 to 50% of the cases.[9–11] In lung cancer patients, worsening pulmonary symptoms may be attributed to advancing cancer leading to delayed diagnosis. In this population, if computed tomographic scans do not suggest either a malignant or thrombotic cause for worsening symptoms, MG must be considered and investigated urgently. Delayed diagnosis may lead to rapid progression and respiratory failure requiring intubation and mechanical ventilation with ventilation rates as high as 40-50% reported in some series.[9–13]

AChR and muscle-specific tyrosine kinase antibodies have been reported to be negative in one-third of patients.[9–12] Furthermore, the characteristic electromyography (EMG) pattern with decrement of muscle action potential with repetitive nerve stimulation which is used to diagnose neuromuscular junction transmission defect is found in less than half of the patients.[9,11,12] Sensitivity of diagnosis can be improved if single fibre EMG is also used; however, this may be difficult to access or perform, particularly during acute MG crisis.

ICI-related MG frequently presents with other ICI-related adverse events, commonly with myositis and/or myocarditis with several reports describing myalgia and/or elevated creatinine phoskinase without a formal diagnosis of myositis.[9] Another common association is ICI-hepatitis.[12] In our series, 11 of our patients developed MG-myositis or MG-myocarditis overlap syndromes and six of those had an overlapping ICI-hepatitis. It is noteworthy that these rates are higher than what is reported in the literature, where the estimated prevalence is 8% and 30% respectively.[9–11] Overlapping ICI-hepatitis observed in 9% and up to 45% to 50% in smaller series.[11–13]

Hospitalization and corticosteroids generally are used for the initial management with close observation. Steroid at a dose of 1 to 2 mg/kg is recommended and often IVIG and/or plasma exchange is used.[7,9–13] Steroids alone might not be adequate considering that these

drugs may take several weeks to show clinical response. Furthermore, in idiopathic MG, the use of very high dose steroids can cause acute transient exacerbation of symptoms.[16,17] Safa et al.,[11] suggest better outcomes for patients who received IVIG or PLEX as first-line treatment compared to those who received steroids alone (95% versus 63% improvement of MG symptoms). In addition, the use of adjunctive steroid-sparing agents has been reported such as mycophenolate mophetil, azathioprine, infliximab or rituximab.[11,13,18] However, these agents also may have a prolonged onset of action.

Complete resolution is rare[9]; Safa et al.,[11] reported the largest analysis of 65 patients with ICI-MG; 19% had complete resolution, 55% had improvement while 26% experienced deterioration and death reported in 37%. ICI-MG is associated with high mortality estimated at approximately 20-28%.[11,18,19] Mortality is notably higher if associated IG-myocarditis is present.[11,14,15]

All of our patients required hospitalization and received IV steroids; 11 patients (69%) received IVIG; 5 underwent plasma exchange; 63% had acetylcholinesterase inhibitors as part of their treatment. Additional immunosuppressants were required in six patients (38%); mycophenolate in three and rituximab and infliximab for one each. We observed only two cases with complete resolution after pulse high dose steroid and early initiation of mycophenolate mophetil. They were the only patients who were able to discontinue steroids. Eight improved with residual symptoms, two experienced initial improvement followed by deterioration, and four worsened despite treatment. Death from ICI-MG was reported in six patients (38%) with a median overall survival rate of 6.3 months (range 1–18.5 mo). The mortality rate is higher than that reported in the literature perhaps because our series has more MG-myositis or myocarditis overlap syndrome; Among the 11 patients with myositis/myocarditis overlap syndrome, six patients died with a median survival of 4.3 months. Of note 3 patients died of progressive cancer, while four died with isolated ICI-MG without evidence of cancer progression. Among the 9 patients with thoracic malignancies, only 4 died with a median survival of 1.8 months (range 0.9–6.6 months).

Conclusions

While limited by a relatively small number and retrospective nature, this study confirms the diagnostic challenges, high morbidity and mortality associated with immunotherapy-induced MG, and emphasizes the need for clinicians to recognize it early in order to initiate appropriate and timely multimodality treatment which is critical to reduce the high mortality rate associated with this rare complication of immunotherapy.

CRediT Authorship Contribution Statement

Abdulrahman Alghabban: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review and editing, Visualization.

Lucy Corke: Resources, Writing - review and editing.

Hans Katzberg: Resources, Writing - review and editing.

Vera Bril: Resources, Writing - review and editing.

Carolina Barnett-Tapia: Resources, Writing - review and editing.

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Penelope Bradbury: Resources, Writing - review and editing.

Geoffrey Liu: Resources, Writing - review and editing.

Natasha Leighl: Resources, Writing - review and editing.

Frances A. Shepherd: Conceptualization, Methodology, Formal analysis, Investigation, Resources, Data curation, Writing - original draft, Writing - review and editing, Visualization, Supervision, Project administration.

Disclosure

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Abcuro; Leadership or fiduciary role with no compensation in GBS/CIDP Foundation of Canada, and MG Society of Canada. Dr. Bril reports receiving grants or support from UCB, Immunovant, CSL, Takeda, Sanofi, Alexion, Momenta, ArgenX, Grifols, Alnylam, Roche, and Janssen; consulting fees from ArgenX, Grifols, CSL, and UCB; honoraria from Takeda, and Grifols; support for attending meetings from Takeda; participation on Data Safety Monitoring Board or Advisory Board from NMDPharma. Dr. Sridhar reports receiving grants or support from Bayer, and Seagen; consulting fees from Astellas, AstraZeneca, Bayer, BMS, Eisai, EMD Serono, Hoffmann-LaRoche, Immunomedics, Ipsen, Janssen, Merck, Pfizer, and Seagen; honoraria from Bayer, EMD Serono, Pfizer, and Seagen; support for attending meetings from EMD Serono, and Janssen. The remaining authors declare no conflict of interest.

References

1. Larkin J, Chiarion-Sileni V, Gonzalez R, et al. Five-year survival with combined nivolumab and ipilimumab in advanced melanoma. *N Engl J Med*. 2019;381:1535–1546.
2. Garassino MC, Gadgeel S, Speranza G, et al. Pembrolizumab plus pemetrexed and platinum in nonsquamous non-small-cell lung cancer: 5-year outcomes from the phase 3 KEYNOTE-189 study. *J Clin Oncol*. 2023;41:1992–1998.
3. Eggermont AMM, Chiarion-Sileni V, Grob JJ, et al. Ipilimumab versus placebo after complete resection of stage III melanoma: long-term follow-up results the EORTC 18071 double-blind phase 3 randomized trial. *J Clin Oncol*. 2019;37:2512.
4. Eggermont AMM, Kicinski M, Blank CU, et al. Five-year analysis of adjuvant pembrolizumab or placebo in Stage III melanoma. *NEJM Evid*. 2022;1:EVIDoa2200214.
5. Felip E, Altorki N, Zhou C, et al. Adjuvant atezolizumab after adjuvant chemotherapy in resected stage IB-IIIA non-small-cell lung cancer (IMpower010): a randomised, multicentre, open-label, phase 3 trial. *Lancet*. 2021;398:1344–1357.
6. Forde PM, Spicer J, Lu S, et al. Neoadjuvant nivolumab plus chemotherapy in resectable lung cancer. *N Engl J Med*. 2022;386:1973–1985.
7. Schneider BJ, Naidoo J, Santomasso BD, et al. Management of immune-related adverse events in patients treated with immune checkpoint inhibitor therapy: ASCO guideline update. *J Clin Oncol*. 2021;39:4073–4126.
8. Cuzzubbo S, Javeri F, Tissier M, et al. Neurological adverse events associated with immune checkpoint inhibitors: review of the literature. *Eur J Cancer*. 2017;73:1–8.
9. Haugh AM, Probasco JC, Johnson DB. Neurologic complications of immune checkpoint inhibitors. *Expert Opin Drug Saf*. 2020;19:479–488.
10. Jordan B, Benesova K, Hassel JC, Wick W, Jordan K. How we identify and treat neuromuscular toxicity induced by immune checkpoint inhibitors. *ESMO Open*. 2021;6:100317.
11. Safa H, Johnson DH, Trinh VA, et al. Immune checkpoint inhibitor related myasthenia gravis: single center experience and systematic review of the literature. *J Immunother Cancer*. 2019;7:319.
12. Eglenen Polat B, Safi D, Hafez M, Kamran A. Pembrolizumab-induced myasthenia gravis: a case report and review of the literature. *Cureus*. 2023;15:e41087.
13. Marco C, Simó M, Alemany M, et al. Myasthenia gravis induced by immune checkpoint inhibitors: an emerging neurotoxicity in neuro-oncology practice: case series. *J Clin Med*. 2022;12:130.
14. Pathak R, Katel A, Massarelli E, Villaflor VM, Sun V, Salgia R. Immune checkpoint inhibitor-induced myocarditis with myositis/myasthenia gravis overlap syndrome: a systematic review of cases. *Oncologist*. 2021;26:1052–1061.
15. Tan S, Day D, Nicholls SJ, Segelov E. Immune checkpoint inhibitor therapy in oncology: current uses and future directions: JACC: CardioOncology state-of-the-art review. *JACC Cardiooncol*. 2022;4:579–597.
16. Guptill JT, Soni M, Meriggioli MN. Current treatment, emerging translational therapies, and new therapeutic targets for autoimmune myasthenia gravis. *Neurotherapeutics*. 2016;13:118–131.
17. Miller RG, Milner-Brown HS, Mirka A. Prednisone-induced worsening of neuromuscular function in myasthenia gravis. *Neurology*. 1986;36:729–732.
18. Zubair AS, Roy B, Baehring JM, Nowak RJ. Myasthenia gravis in the setting of immune checkpoint inhibitor therapy: practical considerations and opinion-based approach to acute management. *Cureus*. 2022;14:e30638.
19. Johnson DB, Manouchehri A, Haugh AM, et al. Neurologic toxicity associated with immune checkpoint inhibitors: a pharmacovigilance study. *J Immunother Cancer*. 2019;7:134.