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# Immune checkpoint inhibitor-induced myasthenia gravis, myositis, and myocarditis overlap syndrome after toripalimab therapy

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## ABSTRACT

**Background:** Immune checkpoint inhibitor-induced myasthenia gravis is an uncommon but potentially fatal immune-related adverse event. It may occur with myositis and myocarditis as a myasthenia-myositis-myocarditis overlap syndrome. Diagnosis can be challenging when antibody and electrophysiological tests are negative.

**Case Presentation:** A 63-year-old man with locally advanced carcinoma of the left buccal mucosa, receiving the programmed death-1 inhibitor toripalimab, presented with fluctuating ptosis, dysarthria, dysphagia, generalized weakness, and breathlessness. He developed type 2 respiratory failure requiring non-invasive ventilatory support. Anti-acetylcholine receptor and anti-muscle-specific kinase antibodies were negative, and repetitive nerve stimulation did not show a classical generalized decremental response but showed a borderline decrement after 1-minute exercise in the orbicularis oculi and deltoid muscles. However, the ocular-bulbar fatigable phenotype with respiratory decline raised strong suspicion of ICI-induced myasthenia gravis. Concurrent elevation of creatine kinase and transaminases supported immune-mediated myositis, while raised high-sensitivity troponin I, creatine kinase-MB, N-terminal pro-B-type natriuretic peptide, echocardiographic abnormalities, and biomarker downward trend after immunomodulation supported probable myocarditis overlap. Imaging excluded major alternative central, neoplastic, and thromboembolic causes. Toripalimab was permanently discontinued. He was treated with intravenous methylprednisolone pulse therapy and intravenous immunoglobulin. After 7 days of treatment, his clinical condition stabilized, non-invasive ventilatory support was removed, and cardiac enzymes showed a down-trending pattern.

**Conclusion:** This case highlights a seronegative and electrophysiologically borderline/atypical presentation of probable toripalimab-associated myasthenia-myositis-myocarditis overlap. Negative antibodies and the absence of a classical repetitive nerve stimulation decrement do not exclude life-threatening ICI-induced myasthenia gravis. Early recognition, prompt withdrawal of the ICI, respiratory support, and immunomodulatory treatment are critical.

**Keywords:** Immune checkpoint inhibitor, toripalimab, seronegative myasthenia gravis, myositis, myocarditis, MMM syndrome, respiratory failure; case report.

**Type of Article:** CASE REPORT **Specialty:** Neurology

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## Background

Immune checkpoint inhibitors (ICIs) have transformed oncology by restoring antitumor T-cell activity through blockade of inhibitory pathways, chiefly CTLA-4, PD-1, and PD-L1. They are being used across multiple malignancies, including head and neck squamous cell carcinoma. They have been accompanied by a broad spectrum of immune-related adverse events (irAEs) [1,2]. Mechanistically, PD-1/PD-L1 and CTLA-4 blockade amplify T-cell activation and cytokine signaling, which improves tumor control but can also precipitate autoimmune injury in non-tumor tissues. CTLA-4 and PD-L1 represent immune checkpoints acting at different levels of the antitumor immune response. CTLA-4 functions mainly during T-cell priming in lymphoid organs by competing with CD28 for CD80/CD86 binding, thereby reducing early T-cell activation. In contrast, PD-L1 acts predominantly in peripheral tissues and within the tumor microenvironment, where its interaction with PD-1 suppresses activated T-cell effector function. Accordingly, CTLA-4 blockade enhances early immune activation, whereas PD-1/PD-L1 blockade primarily restores exhausted effector T-cell responses [3-5].

## Case Presentation

A 63-year-old man with locally advanced carcinoma of the left buccal mucosa was receiving immune checkpoint

inhibitor therapy with toripalimab. The patient received toripalimab 240 mg intravenously, diluted in 100 ml of normal saline and infused over 60 minutes. The last documented toripalimab administration was on 05/02/2026, approximately 35-36 days before admission. He presented with 10 days of drooping of eyelids, slurring of speech, difficulty swallowing, breathlessness, easy fatigability, and generalized weakness. His comorbidities included hypertension, diabetes mellitus, coronary artery disease, and prior percutaneous transluminal angioplasty (PTCA).

On examination, the patient was conscious and oriented, moving all limbs, but had generalized weakness and required non-invasive ventilatory (NIV) support. Neurological examination revealed fluctuating ptosis (right greater than left), flaccid dysarthria, neck flexor weakness, and single-breath count of 12, consistent with ocular, bulbar, and respiratory muscle involvement, suggesting impending myasthenic crisis. A neostigmine challenge (intramuscular dose of 2 mg, under clinical monitoring) produced objective clinical improvement in ptosis, bulbar symptoms, and respiratory effort, supporting the clinical diagnosis of ICI-associated myasthenia gravis. His blood gas analysis at the time of admission showed compensated hypercapnic/type 2 respiratory failure, with pH 7.446, $PaCO_2$ 52.8 mmHg, $PaO_2$ 101 mmHg, and $HCO_3$– 35.8 mmol/L. Respiratory involvement was documented using single-breath count, arterial blood gas analysis, and requirement for NIV support. Because the patient had bulbar weakness with hypercapnic respiratory failure requiring NIV support, the presentation was considered consistent with myasthenic crisis.

Serological work-up showed negative anti-AChR antibody and anti-MuSK antibody. RNS did not show a classical generalized decremental response. However, RNS showed borderline decrement after 1-minute exercise only in orbicularis oculi and deltoid muscles; this decrement improved spontaneously, and no increment was seen after short facilitation or high-frequency RNS. In the setting of recent ICI exposure and a typical subacute fluctuating ocular-bulbar syndrome with respiratory worsening, the impression was suggestive of ICI-induced seronegative myasthenia gravis (particularly because ICI-associated MG can be seronegative and may not always show classical electrophysiological findings early in the course).

There was also strong evidence of overlap myositis and probable myocarditis. Muscle involvement was supported by generalized weakness, neck flexor weakness, CK 1,032 U/L initially with later fall to 191.1 U/L, along with SGPT 256.6 U/L and SGOT 138.9 U/L, supporting inflammatory muscle injury. EMG and muscle MRI were not performed during the acute admission because the patient required urgent respiratory and immunomodulatory management. Myositis antibody testing was considered but was not performed during the acute admission.

Cardiac involvement was classified as probable ICI-associated myocarditis overlap rather than histologically definite myocarditis. It was supported by high-sensitivity troponin I 79.4 pg/ml on admission, persistent elevation to 68.10 pg/ml during hospitalization, and subsequent decline to 27.5 pg/ml after immunomodulation; CPK-MB was markedly elevated at 48.9 ng/ml, with NT-proBNP 258 pg/ml. ECG showed sinus tachycardia with a short PR interval, a borderline ECG. Echocardiography showed

***Table 1.*** *Concise case timeline showing ICI exposure, symptom onset, diagnostic tests, treatment, and outcome.*

| Time point | Clinical finding |
|---|---|
| Pre-ICI period | Locally advanced carcinoma of the left buccal mucosa. |
| ICI exposure | Toripalimab 240 mg IV in 100 ml of normal saline over 60 minutes; at least two administrations documented in the available slips. |
| Approximately 35 days before admission | Last documented toripalimab administration. |
| 10 days before admission | Drooping of eyelids, slurring of speech, dysphagia, breathlessness, fatigability, and generalized weakness. |
| At admission | Fluctuating bilateral ptosis, flaccid dysarthria, neck flexor weakness, single-breath count of 12, and need for NIV. ABG: pH 7.446, $pCO_2$ 52.8 mmHg, $pO_2$ 101 mmHg, $HCO_3^-$ 35.8 mmol/l. |
| During admission | Neostigmine challenge 2 mg IM with objective clinical improvement; anti-AChR and anti-MuSK antibodies negative. |
| During admission | RNS: borderline decrement after 1-minute exercise in the orbicularis oculi and deltoid; no classical generalized decrement. |
| During admission | CK 1032 U/l with decline to 191.1 U/l; SGPT 256.6 U/l; SGOT 138.9 U/l. |
| During admission | Troponin I 79.4 -> 68.10 -> 27.5 pg/ml; CK-MB 48.9 ng/ml; NT-proBNP 258 pg/ml. |
| Cardiac evaluation | ECG: sinus tachycardia/short PR/borderline ECG. Echo: LVEF 45%, inferior and posterior wall hypokinesia, grade I LVDD, mild MR/TR, no pericardial effusion. |
| Treatment period 7 days | high-dose IV methylprednisolone pulse therapy (1g/day for 6 days), IVIG (140g) over 5 days, and NIV support. |
| After approximately 7 days | Clinical stabilization, NIV removed, and cardiac enzymes showed a downward trend. |

***Table 2**. Key clinical, laboratory, imaging, and treatment findings.*

| Category | Finding | Result |
|---|---|---|
| Clinical trigger | Immune checkpoint inhibitor exposure | Toripalimab 240 mg IV; last documented dose approximately 35 days before admission. |
| Cancer diagnosis | Oral cavity malignancy | Locally advanced left buccal mucosa carcinoma. |
| Presenting symptoms | Ptosis, slurred speech, dysphagia, breathlessness, fatigability, generalized weakness | Present. |
| Examination | Fluctuating ptosis, flaccid dysarthria, neck flexor weakness | Present |
| Respiratory involvement | Single-breath count | 12 |
| Respiratory status | ABG and ventilatory support | pH 7.446, $pCO_2$ 52.8 mmHg, $pO_2$ 101 mmHg, $HCO_3^-$ 35.8 mmol/l; type 2 respiratory failure; on NIV |
| Neostigmine challenge | Dose and response | 2 mg intramuscular; objective improvement in ptosis, bulbar symptoms, and respiratory effort |
| Serology | Anti-AChR antibody | Negative |
| Serology | Anti-MuSK antibody | Negative |
| Electrophysiology | Repetitive nerve stimulation test | Borderline decrement after 1-minute exercise in the orbicularis oculi and deltoid; no classical generalized decrement |
| CNS imaging | NCCT head | Normal |
| Vascular chest imaging | CT pulmonary angiography | Normal |
| CT chest and abdomen | Thymus | Normal |
| Muscle injury | Creatine kinase | 1032 U/L initially; later 191.1 U/L |
| Muscle and liver enzymes | SGPT/SGOT | SGPT 256.6 U/L; SGOT 138.9 U/L |
| Myocardial injury | Troponin I | 79.4 pg/ml, 68.10 pg/ml, 27.5 pg/ml |
| Cardiac enzyme | CPK-MB | 48.9 ng/ml |
| Cardiac strain | NT-proBNP | 258 pg/ml |
| ECG | Rhythm<br>conduction | Sinus tachycardia, short PR interval, borderline ECG; no documented ST-elevation MI in available record |
| Echocardiography | LV function and wall motion | LVEF 45%; inferior and posterior wall hypokinesia; grade I LVDD; mild MR/TR; RVSP approximately 35 mmHg; no clot/mass/vegetation; no pericardial effusion |
| Cardiac MRI/biopsy | Confirmatory testing | Not performed |
| Infection exclusion | C. difficile GeneXpert | Negative |
| Clinical diagnosis by treating team | Myasthenic crisis, myositis, probable myocarditis overlap | clinically inferred |
| Treatment | Immunomodulation and support | Toripalimab permanently stopped; high-dose IV methylprednisolone pulse therapy; IVIG (140 g) over 5 days; NIV support |
| Outcome | Clinical and biochemical response | Stabilized after approximately 7 days; NIV removed; cardiac enzymes showed a down-trending. |

LVEF 45%, inferior and posterior wall hypokinesia, grade I LV diastolic dysfunction, mild mitral regurgitation, mild tricuspid regurgitation, RVSP around 35 mmHg, no intracardiac clot or vegetation, and no pericardial effusion. In view of prior coronary artery disease and PCI, acute coronary syndrome, demand ischemia, and ischemic cardiomyopathy were considered important differentials. There was no documented ST-elevation myocardial infarction in the available ECG record. Cardiac MRI, coronary angiography, and endomyocardial biopsy were not performed; therefore, the cardiac component was classified as probable ICI-associated myocarditis overlap, not definite myocarditis.

Neuroimaging and thoracic imaging were not suggestive of an alternative central or thromboembolic cause: NCCT (non-contrast computed tomography) head was normal, CT pulmonary angiography was normal, CT chest

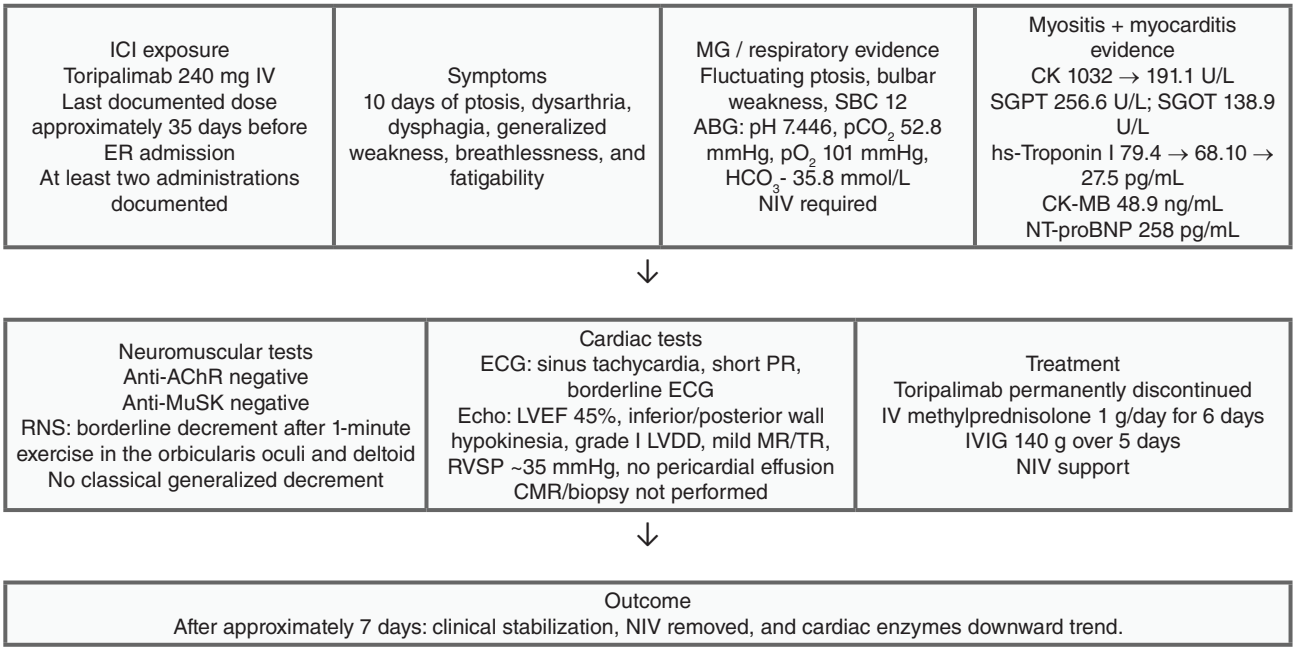



***Figure 1**. Clinical profile and management pathway of the patient.*

showed a left lower lobe atelectatic band, and thymus was normal.

Toripalimab was permanently discontinued. The patient completed 5 days of IVIG (140 G) and had also received high-dose intravenous methylprednisolone pulse therapy (1G/day for 6 days) during admission. The patient required NIV during the acute phase and was weaned after clinical stabilization. After approximately 7 days of treatment, his clinical condition stabilized, NIV was removed, and cardiac enzymes showed a down-trending pattern. Further cancer treatment was planned to be decided by the treating oncology team, avoiding further toripalimab exposure because of the severe immune-related adverse event. The key timeline, diagnostic, laboratory, imaging, and treatment details are summarized in Tables 1 and 2.

## Discussion

Neurologic irAEs are uncommon compared with dermatologic, endocrine, or gastrointestinal toxicities, but they are clinically important because they may progress rapidly and can be fatal. Among these, ICI-induced myasthenia gravis (irMG) is rare, with a reported incidence generally below 1%, yet it carries disproportionately high morbidity and mortality [1,2,6]. A distinctive feature of irMG is its tendency to occur not in isolation but as part of an overlap syndrome with myositis and/or myocarditis, termed MMM overlap syndrome. Recent clinical reviews emphasize that bulbar symptoms, respiratory decline, and biochemical evidence of skeletal and cardiac muscle injury should trigger urgent evaluation for combined disease [2,7]. Figure 1 illustrates the patient's clinical profile and management pathway.

In the present case, the diagnosis was classified as probable toripalimab-associated myasthenia gravis-myositis-myocarditis overlap syndrome rather than definite MMM overlap syndrome. This cautious classification was used because cardiac MRI and endomyocardial biopsy were not performed, and because pre-existing coronary artery disease with prior PCI created a competing ischemic differential for myocardial injury. Nevertheless, the temporal association with toripalimab, acute ocular-bulbar fatigable weakness, hypercapnic respiratory failure, biochemical myositis, myocardial biomarker elevation, echocardiographic LV dysfunction, and response after ICI withdrawal and immunomodulation supported an immune-mediated overlap phenotype.

According to the literature, ICI-associated MG may be seronegative and may lack a classical decremental pattern on repetitive nerve stimulation. Recent case reports and reviews describe patients with negative AChR and MuSK antibodies and even uninformative electrodiagnostic studies, yet with a compelling clinicobiological syndrome consistent with irMG. Therefore, a negative antibody panel or absent of a classical decrement on repetitive nerve stimulation does not exclude the diagnosis, particularly in the setting of recent ICI exposure, fluctuating ocular-bulbar weakness, respiratory compromise, and concurrent myositis/myocarditis markers. This is especially relevant to our case, where AChR and MuSK antibodies were negative, and RNS showed only borderline/atypical decremental findings [1,2,6,8].

The myocarditis component is of particular prognostic importance. In ICI overlap syndrome, troponin elevation may be the earliest indicator of cardiac involvement, even before arrhythmia or heart failure develops. In our patient,

the myocardial component was supported by serial troponin elevation with downward trend after immunomodulation, raised CK-MB and NT-proBNP, sinus tachycardia/short PR interval on ECG, and echocardiographic LVEF reduction with regional wall-motion abnormality. However, because of pre-existing coronary artery disease, the cardiac diagnosis was worded as probable myocarditis overlap rather than definite myocarditis. In parallel, CK elevation with transaminitis may reflect associated myositis rather than isolated hepatic injury, especially when AST/ALT rise in the context of profound muscle involvement [7,9].

Management recommendations in the literature stress immediate discontinuation of the offending ICI and early aggressive immunosuppression. High-dose corticosteroids remain first-line therapy, but many authors emphasize that patients with bulbar weakness, respiratory decline, myocarditis, or marked CK/troponin elevation should receive IVIG or plasma exchange early, rather than waiting for steroid response alone. Recent reports also describe escalation therapies such as rituximab or tocilizumab in refractory cases, although evidence remains limited and largely case-based [8].

Taken together, the literature supports the interpretation that patients receiving PD-1/PD-L1 or CTLA-4 blockade who develop acute or subacute ocular-bulbar weakness, particularly with respiratory symptoms, should be screened promptly for myositis and myocarditis overlap using CK, AST, ALT, troponin, CPK-MB, ECG, echocardiography, and respiratory assessment. The diagnosis remains primarily clinical, and neither seronegativity nor nondiagnostic RNS excludes it. In that context, our patient's recent toripalimab exposure, subacute fluctuating ptosis-dysarthria-dysphagia-breathlessness, negative AChR and MuSK antibodies, borderline RNS, marked CK elevation, SGPT/SGOT elevation, dynamic troponin rise, and echocardiographic LV dysfunction fit within the increasingly recognized spectrum of probable ICI-induced seronegative MG with myositis-myocarditis overlap syndrome [1,2,6-8].

### What's new?

This case highlights that toripalimab-associated myasthenia myositis myocarditis overlap syndrome may present with negative AChR and MuSK antibodies and only borderline abnormalities on repetitive nerve stimulation. A compatible fatigable ocular bulbar phenotype, respiratory deterioration, and concurrent skeletal- and cardiac-muscle biomarker abnormalities should prompt urgent treatment despite inconclusive serological or electrophysiological findings.

### Acknowledgment

Nil.

### List of Abbreviations

| | |
|---|---|
| ABG | Arterial blood gas |
| AChR | Acetylcholine receptor |
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CAD | Coronary artery disease |
| CK | Creatine kinase |
| CK-MB | Creatine kinase-MB |
| CMR | Cardiac magnetic resonance |
| CT | Computed tomography |
| CTLA-4 | Cytotoxic T-lymphocyte-associated protein 4 |
| ECG | Electrocardiogram/electrocardiography |
| EMG | Electromyography |
| hs-troponin I | High-sensitivity troponin I |
| ICI | Immune checkpoint inhibitor |
| irAE | Immune-related adverse event |
| irMG | Immune checkpoint inhibitor-associated myasthenia gravis |
| IV | Intravenous |
| IVIG | Intravenous immunoglobulin |
| LV | Left ventricular |
| LVDD | Left ventricular diastolic dysfunction |
| LVEF | Left ventricular ejection fraction |
| MG | Myasthenia gravis |
| MMM | Myasthenia–myositis–myocarditis |
| MR | Mitral regurgitation |
| MuSK | Muscle-specific kinase |
| NCCT | Non-contrast computed tomography |
| NIV | Non-invasive ventilation |
| NT-proBNP | N-terminal pro-B-type natriuretic peptide |
| PCI | Percutaneous coronary intervention |
| PD-1 | Programmed cell death protein 1 |
| PD-L1 | Programmed death-ligand 1 |
| RNS | Repetitive nerve stimulation |
| RVSP | Right ventricular systolic pressure |
| SBC | Single-breath count |
| TR | Tricuspid regurgitation |

### Conflict of interest

The authors declare that they have no conflicts of interest regarding the publication of this case report.

### Funding

This study was not supported by any sponsor or funder.

### Consent for publication

Written informed consent was obtained from the patient for publication of the details of this medical case and any accompanying images.

### Data availability statement

All data generated or analyzed during this study are included in this article. Furthermore, details are not publicly available due to patient confidentiality but may be made available by the corresponding author on reasonable request, subject to ethical and privacy considerations.

### Ethical approval

Ethical approval was not required for this single case report in accordance with local institutional policy.

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## Summary of case

| Item | Details |
|---|---|
| Patient | 63-year-old male |
| Final diagnosis | Probable toripalimab-induced seronegative myasthenia gravis with myositis-myocarditis overlap / MMM syndrome |
| Symptoms | Fluctuating ptosis, dysarthria, dysphagia, generalized weakness, breathlessness, type 2 respiratory failure |
| Medications | Toripalimab; intravenous methylprednisolone pulse therapy; intravenous immunoglobulin |
| Clinical procedure | Non-invasive ventilatory support, antibody testing, repetitive nerve stimulation, cardiac biomarker testing, muscle enzyme testing, ECG, echocardiography, neuroimaging, thoracic imaging, permanent discontinuation of toripalimab |
| Outcome | Stable after approximately 7 days of intravenous methylprednisolone pulse therapy and IVIG; NIV removed; cardiac enzymes downward trend |
| Specialty | Neurology / Neuroimmunology / Oncology |