Immune checkpoint inhibitor-induced myocarditis with myositis and/or myasthenia gravis overlap syndrome: A case series

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Abstract. Immune checkpoint inhibitors (ICIs) can lead to immune-related adverse events, including myocarditis with myositis and/or myasthenia gravis overlap syndrome (IM3OS). This syndrome poses notable management challenges and has high mortality rates. Due to limited data, its clinical features and optimal treatment strategies remain poorly understood. The present study aims to clarify these aspects and share clinical management experiences. A total of 6 patients with IM3OS were retrospectively analyzed, collecting demographic, clinical, laboratory, electrophysiological, therapeutic and outcome data. Additionally, the relevant literature was reviewed to contextualize the findings. The 6 patients, all male, with a median age of 70.5 years (range, 63-83 years), developed symptoms a median of 30.5 days post-ICI initiation. Common symptoms included fluctuating ptosis, neck weakness, fatigue, myalgia, diplopia, dysphagia, dysarthria and limb weakness. Of the 6 patients, 3 required ventilation support. Elevated creatine kinase (CK) and cardiac troponin I (cTnI) were observed in all patients, with CK and cTnI levels decreasing rapidly post-treatment. Cardiac troponin T levels remained elevated for 3 months. Myotonic discharge and increased jitter were noted in 2 patients. Treatments included corticosteroids, intravenous immunoglobulin (IVIG), plasmapheresis and rituximab. Pyridostigmine was discontinued in 2 out of 4 patients due to severe cardiac adverse effects. Despite interventions, 2 patients died and 1 was bedridden, with only 3 showing favorable outcomes. In conclusion, IM3OS has a high fatality rate, highlighting the need for prompt intervention in ICI-treated patients with neuromuscular symptoms. Serum cTnI is a reliable cardiac injury marker, and early treatment with IVIG, plasmapheresis and high-dose methylprednisolone is recommended. Pyridostigmine should be administered with caution in patients with IM3OS, particularly in the presence of bradyarrhythmic ICI-related myocarditis. Given the high mortality and disability rates associated with IM3OS, novel biological targeted therapies such as eculizumab and efgartigimod may reduce fatal outcomes.

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies (mAbs) used in cancer immunotherapy; they enhance the ability of the immune system to kill cancer cells by targeting programmed cell death receptor 1 (PD-1), programmed cell death ligand 1 (PD-L1) and cytotoxic T lymphocyte-associated antigen 4 on immune cells (1-3). ICIs have revolutionized cancer treatment, markedly improving overall survival rates in patients with various advanced malignancies, including melanoma, non-small cell lung cancer, renal cell carcinoma and Hodgkin's lymphoma (2,3). However, their immune-enhancing mechanism can trigger systemic T-cell responses, leading to a spectrum of autoimmune toxicities known as immune-related adverse events (irAEs) (2,4). These irAEs can affect various tissues or organs throughout the body (3). Neurological irAEs, although rare, can be life-threatening and often manifest as neuromuscular disorders such as myasthenia gravis (MG) and myositis. Since its initial description in 2017 (5), the co-occurrence of ICI-related myocarditis with myositis and/or MG overlap syndrome (IM3OS) has been increasingly reported, posing unique diagnostic and management challenges (6-14). However, due to limited data and case reports, the clinical features, pathogenesis and optimal treatment strategies for this condition remain poorly understood.

The present study retrospectively summarized the demographic, clinical, laboratory, electrophysiological, therapeutic and outcome data of 6 patients with IM3OS to improve early recognition and provide better management and outcomes for patients experiencing neurological irAEs. Through a comprehensive literature review, the study aims to enhance understanding of IM3OS by investigating its potential mechanisms, diagnostic approaches and treatment strategies.

Patients and methods

Patient selection. The medical records of patients treated with ICIs in the China-Japan Friendship Hospital (Beijing, China) between September 2020 and July 2025 were reviewed. The inclusion criteria of the study were as follows: i) ≥18 years old; ii) receipt of ICI therapy; and iii) a diagnosis of either myositis or MG in combination with myocarditis. The exclusion criteria were as follows: i) Pre-existing myocarditis, myositis or MG prior to ICI initiation; and ii) incomplete medical records or loss to follow-up. The definitions of ICI-related (ir)Myocarditis, irMyositis and irMG were based on the consensus statements from the International Cardio-Oncology Society (IC-OS) (15) and the study by Guidon *et al* (16). Patients were classified into possible, probable or definite categories for myositis and MG according to the established criteria. Definite irMG required positive acetylcholine receptor (AChR) or muscle-specific kinase (MuSK) antibody results plus electrodiagnostic evidence. Probable irMG required any one of the following: Positive AChR or MuSK antibody results, abnormal electrodiagnostic findings, or unequivocal clinical response to cholinesterase inhibitors. Possible irMG was defined by negative AChR or MuSK antibody results/a lack of testing, absent electrodiagnostic abnormalities/a lack of testing and a normal creatine kinase (CK) level (16). Patients with elevated CK and no MG evidence were considered for irMyopathy (16). Definite irMyositis required any of the following: i) Muscle biopsy or autopsy findings consistent with myositis or immune-mediated necrotizing myopathy; ii) electromyography (EMG) showing fibrillation potentials/positive sharp waves with myopathic motor unit potentials; or iii) muscle magnetic resonance imaging (MRI) showing short τ inversion recovery hyperintensity or contrast enhancement combined with EMG findings of myopathic motor units. Probable irMyositis required any one of the following: EMG findings of myopathic motor units, MRI abnormalities or elevated CK. Possible irMyositis was defined as a compatible history and examination within the irAE timeframe without further workup, or inconclusive workup with no alternative explanation for symptoms (16). Overall, 6 patients met all the inclusion criteria and none of the exclusion criteria, and were recruited for the study. Among them, all patients met with the IC-OS ICIs-induced myocarditis clinical diagnosis and met the probable ICIs-induced myositis diagnostic criteria; 1 patient met the probable irMG diagnostic criteria, while the remaining 5 patients met all other criteria for possible irMG, with the sole exception of elevated CK.

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Trial Ethics Committee of China-Japan Friendship Hospital (approval no. 2019-166-K115) on November 6, 2019, and written informed consent was obtained from all patients or their legal guardians.

Clinical data collection. Demographic information, clinical presentations and treatment details were retrospectively collected and analyzed. Clinical data included symptoms at presentation, the timeline of symptom development and the response to treatment. The severity of symptoms and effectiveness of therapy were assessed using the Medical Research Council (MRC) (17) and MG-Activity of Daily Living (MG-ADL) (18) scores.

Laboratory data collection. Laboratory data included levels of CK and cardiac biomarkers such as cardiac troponin I (cTnI) and cardiac troponin T (cTnT). CK levels were measured using the AU5800 Clinical Chemistry Analyzer (Beckman Coulter, Inc.), which employs enzymatic technology. Troponin T levels were assessed using the Cobas e801 analyzer (Roche Diagnostics GmbH), which employs electrochemiluminescence immunoassay technology. Troponin I levels were assessed using the UniCel DXI800 Clinical Chemistry Analyzer (Beckman Coulter, Inc.), which employs chemiluminescence immunoassay technology. These biomarkers were regularly monitored to assess muscle damage and cardiac injury. Serological testing comprised enzyme-linked immunosorbent assay for anti-AChR antibodies, a cell-based assay for anti-MuSK antibodies, and radioimmunoassay for anti-voltage-gated calcium channel (VGCC) antibodies.

Electrophysiological data collection. Electrophysiological examinations, including sensory and motor nerve conduction, needle electromyography, repetitive nerve stimulation (RNS) and frontalis muscle concentric needle electrode single fiber EMG (SF-EMG), were performed using Keypoint workstation (software version 2.10; Dantec Dynamics).

Literature review. To provide a comprehensive discussion on IM3OS, a thorough literature review of case series was conducted using PubMed (https://pubmed.ncbi.nlm.nih.gov/). The search key words included 'IM3OS', 'triple M syndrome', 'immune checkpoint inhibitor', 'myasthenia gravis', 'myositis' and 'myocarditis'. The inclusion criteria were: i) Case series (≥3 cases) of IM3OS (triple M syndrome); and ii) articles published in English. The exclusion criteria were: i) Single case reports; ii) reviews, editorials or conference abstracts without original data; and iii) studies without sufficient clinical data for analysis. Relevant studies were carefully reviewed to gain insights into the potential mechanisms, diagnostic approaches, treatment strategies and outcomes associated with IM3OS.

Statistical analysis. Descriptive statistics were used to summarize the demographic, clinical, laboratory and treatment data of the patients. The median and range were calculated for continuous variables, while frequencies and percentages were used for categorical variables. All data analysis was performed using Microsoft Excel for Microsoft 365 MSO (Version 2606) (Microsoft Corporation). Specifically, the software was used for data tabulation, calculation of descriptive statistics and preparation of the graphical presentation. No inferential statistical tests were applied given the descriptive nature of this case series.

Results

Demographics data. All 6 patients were male, with a median age of 70.5 years old (range, 63-83 years). The patients had various types of cancer (Table I): 2 had pulmonary adenocarcinoma, 2 had esophageal cancer, 1 had a bladder tumor and 1 had rectal cancer. All 6 patients had received either a single dose or two doses of ICI: 2 received tislelizumab (an anti-PD-1 mAb), 2 received sintilimab (an anti-PD-1 mAb), 1 received pembrolizumab, and 1 received atezolizumab

Table I. Summary of symptoms, treatment and outcome of the 6 patients.

A, Patient details

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age, years	67	83	63	66	74	81
Sex	Male	Male	Male	Male	Male	Male
Indication	Esophageal cancer	Bladder tumor	Pulmonary adenocarcinoma	Pulmonary adenocarcinoma	Rectal cancer	Esophageal cancer
ICI	Tislelizumab	Tislelizumab	Sintilimab, Atezolizumab	Sintilimab	Pembrolizumab	Sintilimab
Mechanism	PD-1	PD-1	PD-1, PD-L1	PD-1	PD-1, PD-L1	PD-1
Time interval between ICI initiation and onset, days	23	42	36	29	32	18
Time interval between onset and admission, days	4	8	14	11	2	5

B, Symptoms

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Ptosis	+	+	+	+	+	+
Diplopia	+	-	+	+	+	-
Dysphagia	-	+	+	-	+	+
Dysarthria	-	+	+	-	+	+
Neck weakness	+	+	+	-	+	+
Neck MRC score	4/5	4/5	2/5	5/5	2/5	2/5
Limb weakness	-	-	+	-	+	+
Limb MRC score	5/5	5/5	4/5	5/5	4/5	3/5
Myalgia	+	-	+	-	+	+
Fatigue	+	+	+	-	+	+
Dyspnea	-	-	+	-	+	+
Chest distress	-	+	+	-	+	+
Orthopnea	-	-	+	-	+	+
Palpitation	-	-	+	-	+	+
Ventilation support	-	-	+	-	+	+
Peak MG-ADL	10	11	23	6	22	21

C, Myositis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Peak CK, U/l	5,735	3,665	2,517	1,015	4,399	11,940
EMG	Myotonic discharge in the sternocleidomastoid muscle	Normal	Not performed	Normal	Myotonic discharge in the sternocleidomastoid muscle	Not performed
Diagnosis	Probable	Probable	Probable	Probable	Probable	Probable

D, MG

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Fluctuating	Yes	Yes	Yes	Yes	Yes	Yes

Table I. Continued.

D, MG

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Fatigue test	Eye fatigue test: Positive	Eye fatigue test and ice-pack test: Positive	Arm fatigue test: Positive	Eye fatigue test and ice-pack test: Positive	Eye fatigue test: Positive	Eye fatigue test: Positive
MG antibody	Not done	Normal	Not done	Not done	Positive	Not done
RNS	Normal	Normal	Not done	Normal	Normal	Not done
SF-EMG	Increased jitter	Not done	Not done	Normal	Increased jitter	Not done
Diagnosis	-	-	-	-	Probable	-

E, Myocarditis

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Peak cTnI/cTnT, ng/ml	cTnI, 4.4906	cTnI, 0.397	cTnI, 0.511	cTnI, 0.123	cTnT, 1.77	cTnI, 23.592
ECG	Prolonged PR interval and ST-T deviation	Bradycardia, paroxysmal atrial fibrillation and ST-T deviation	Sinus tachycardia, premature ventricular contractions and ST-T deviation	Normalz	Bradycardia, paroxysmal atrial fibrillation	Paroxysmal atrial fibrillation, bundle branch block and ST-T deviation
Diagnosis	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis	Clinical diagnosis

F, Treatment

Parameter	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Corticosteroids	IVMP, 240 mg/day	IVMP, 80 mg/day	IVMP, 1,000 mg/day	IVMP, 80 mg/day	IVMP, 80 mg/day	IVMP, 500 mg/day
Plasmapheresis	No	Twice	No	No	No	
IVIG	No	No	0.4 g/kg/day for 7 days	No	0.4 g/kg/day for 15 days	0.4 g/kg/day for 5 days
Immunosuppressive agents	No	No	No	No	No	RTX 500 mg
Pyridostigmine bromide	Intolerant	Intolerant	No	Yes	Yes	No
Length of stay in hospital, days	19	16	48	9	90	11
Outcome	Only mild neck fatigue and ptosis at 1 month	Only mild dysphagia and ptosis at 2 months	Ventilator was withdrawn, gradually recovered; succumbed to pneumonia at 3 months	Only mild ptosis at 1 month	Ventilator was withdrawn, gradually recovered; remained bedridden at 3 months	Succumbed at 2 weeks
Tumor	Stable	Tumor relapsed	-	Stable	Tumor relapsed	-

ICI, immune checkpoint inhibitor; PD-1, programmed cell death receptor 1; PD-L1, programmed cell death ligand 1; MG-ADL, myasthenia gravis-activity of daily living scale; CK, creatine kinase; EMG, electromyography; RNS, repetitive nerve stimulation; SF-EMG, single-fiber EMG; cTnI, cardiac troponin I; ECG, electrocardiogram; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; RTX, rituximab; cTnT, cardiac troponin T; MRC, Medical Research Council.

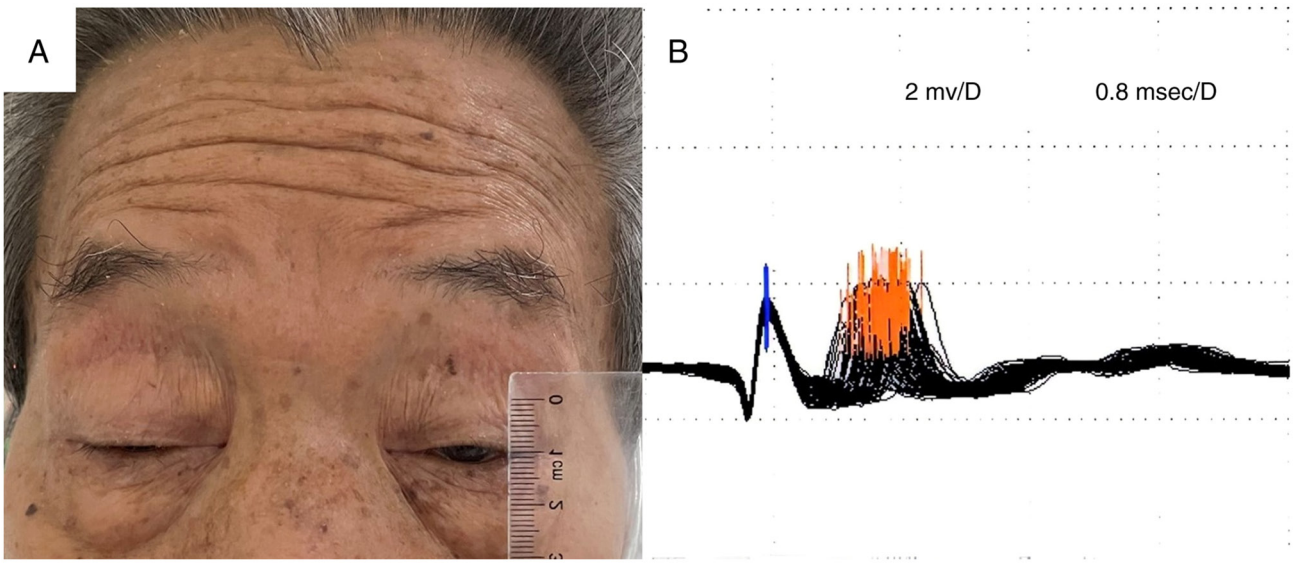

Figure 1. Ocular and electrophysiological findings in patients with myocarditis with myositis and/or myasthenia gravis overlap syndrome. (A) Ptosis of case 2. (B) Increased jitter in single fiber electromyography of case 1. mv/D, millivolts per division.

(an anti-PD-L1 mAb) and sintilimab. The median time interval between initiating ICIs and disease onset was 30.5 days (range, 18-42 days). The median time interval between onset and admission was 6.5 days (range, 2-14 days).

Clinical features and laboratory findings. The symptoms of the 6 patients are summarized in Table I. All patients had fluctuating ptosis (Fig. 1) and positive eyelid fatigue tests. Other common symptoms included neck weakness (5/6), generalized fatigue (5/6), myalgia (4/6), diplopia (4/6), dysphagia (4/6), dysarthria (4/6) and limb weakness (3/6). Of the 6 patients, 3 had dyspnea and needed ventilation support. The median peak MRC score of all the patients' neck muscles was 3.0 (range, 2-5), while the limb muscles' median score was 4.5 (range, 3-5). The peak MG-ADL scores ranged from 6 to 24 (median, 16) (Table I).

All patients had elevated CK levels, ranging from 1,015 to 11,940 U/l (median, 4,032 U/l). In total, 3 patients (cases 3, 5 and 6) had MG-ADL scores >20, had dyspnea and needed ventilation support, but their CK levels varied greatly, ranging from 2,517 to 11,940 U/l. All the patients met the probable ICI-induced myositis diagnostic criteria. The median CK level peak time was 2.5 days (range, 1-13 days) from disease onset, and the median MG-ADL score peak time was 4.0 days (range, 1-17 days) from disease onset. The median time interval between disease onset and medication was 7.5 days (range, 4-15 days). After treatment, CK levels in all patients decreased markedly, but clinical symptoms did not improve or even deteriorate (Fig. 2A-F).

Laboratory tests showed elevated cTnI and/or cTnT levels, as represented in Table I and Fig. 2. cTnT and cTnI were monitored simultaneously in 4 patients. All 6 patients had elevated troponin levels, with cTnI ranging from 0.123-23.592 ng/ml (median, 0.511 ng/ml). All 6 cases met the IC-OS ICIs-induced myocarditis clinical diagnosis. As the symptoms improved and MG-ADL scores decreased, CK and cTnI underwent a noticeable decline, but the cTnT elevation persisted (case 1) (Fig. 2A) and even continued to rise (cases 2, 3, 4 and 5) (Fig. 2B-E). Except for case 5, whose cTnI was not tested, and case 6, whose follow-up time was only 15 days, in cases 1-4 (Fig. 2A-D), cTnI levels dropped into the normal range (<0.0198 ng/ml) within 1 month. However, despite varying follow-up durations among the 6 patients, cTnT levels at the final follow-up did not return to the normal range (<0.014 ng/ml) in any patients, with fluctuations around 0.5 ng/ml (Fig. 2A-F). cTnT levels of case 5 remained around 0.5 ng/ml after a follow-up of 3 months (Fig. 2E).

In total, 5 of the patients had an abnormal electrocardiogram (ECG), which revealed a new conduction delay with a prolonged P-R interval (240 msec), ST-T deviation, bradycardia, paroxysmal atrial fibrillation, sinus tachycardia (120 bpm), and premature ventricular contractions (Table I).

Of the 6 patients, 4 patients (cases 1, 2, 4 and 5) underwent nerve conduction studies and needle electromyography, with 3 (cases 1, 2 and 4) conducted within 10 days after disease onset and 1 (case 5) at 40 days. None had a notable decrease in low-frequency RNS. The 2 patients (cases 1 and 5) with higher CK levels had myotonic discharge in the sternocleidomastoid muscle, but none showed myopathological changes. Concentric SF-EMG was performed in 3 patients, and 2 showed increased jitter (Fig. 1B).

Only 2 patients (cases 2 and 5) underwent testing for the anti-AChR, anti-VGCC and anti-MuSK antibodies, with 1 patient (case 5) showing positive anti-AChR antibody results. Case 5 met the probable ICIs-induced MG diagnostic criteria.

Treatment and outcomes. ICI therapy was discontinued immediately after diagnosing IM3OS in all 6 patients. All the patients were treated with different doses of corticosteroids. The intravenous methylprednisolone dose ranged from 80 to 1,000 mg/day, which was followed by a tapering dose of oral prednisone. In combination with corticosteroids, 3 patients received intravenous immunoglobulin (IVIG), 1 received plasmapheresis and 1 received rituximab. A total of 3 patients

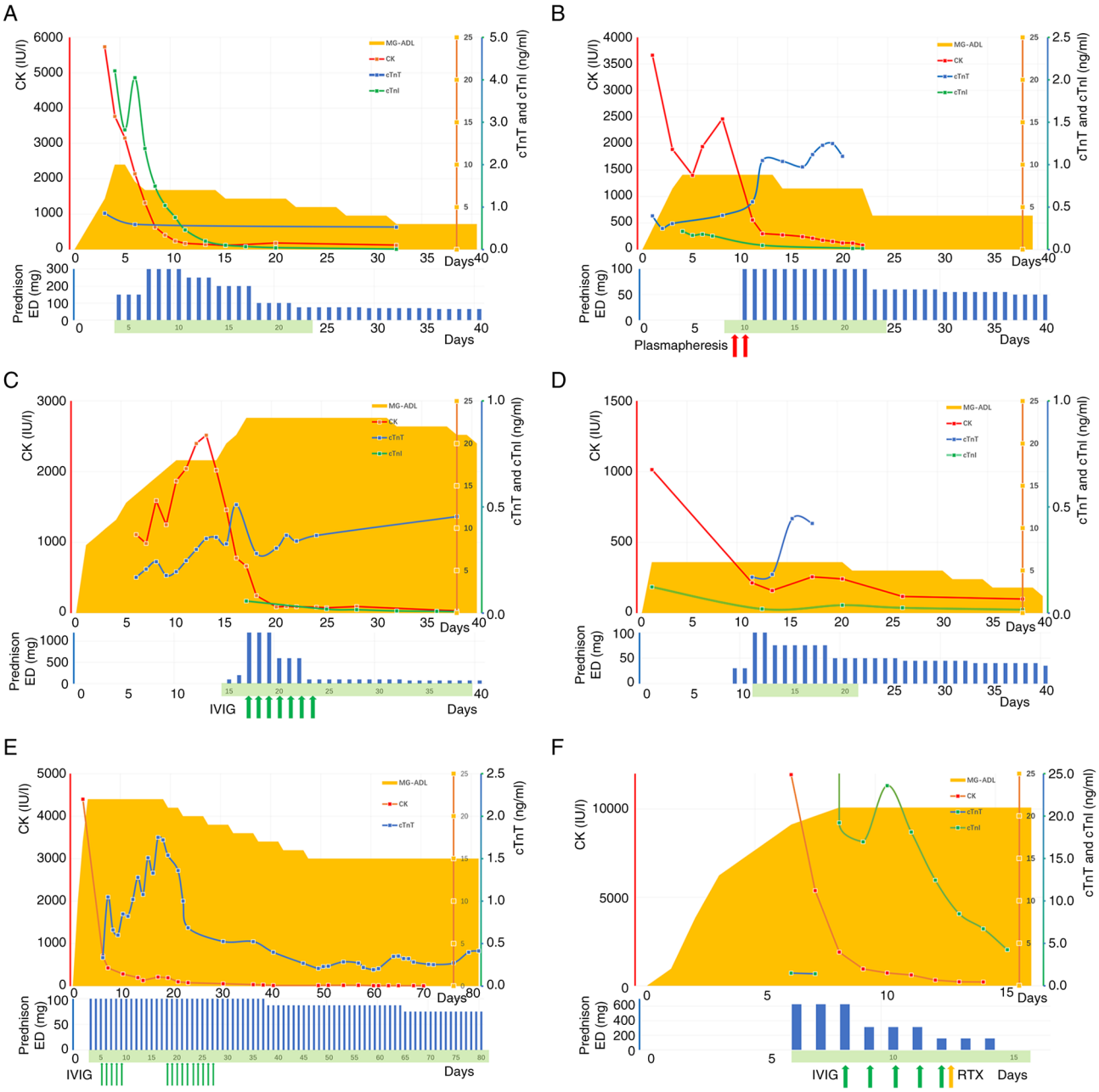

Figure 2. Longitudinal clinical and biomarker profiles of 6 IM3OS cases. (A) Case 1, (B) case 2, (C) case 3, (D) case 4, (E) case 5 and (F) case 6 biomarkers throughout the disease course. The timeline (x-axis) is aligned to the day of symptom onset (day 0); green-shaded segments indicate the duration of hospitalization (admission occurred on days 4, 8, 14, 11, 2 and 5 for cases 1-6, respectively). The left y-axis shows serum CK levels (IU/l), and the right y-axis displays MG-ADL scores as well as cTnI and cTnT concentrations (ng/ml). Key therapeutic interventions, including corticosteroids (presented as prednisone-equivalent daily dose), IVIG, plasmapheresis and RTX, are annotated along the timeline. After treatment, CK levels in all patients decreased markedly, but MG-ADL scores did not improve or even deteriorate. After treatment, both CK and cTnI decreased markedly in most patients. By contrast, (A) cTnT elevation persisted in case 1 and (B-E) continued to rise in cases 2-5. (A-D) In cases 1-4, cTnI levels fell below the upper reference limit (<0.0198 ng/ml) within 1 month, whereas (A-F) cTnT remained above its upper reference limit (<0.014 ng/ml) throughout follow-up, despite varying follow-up durations, fluctuating around 0.5 ng/ml at final follow-up. (E) In case 5, cTnT remained at ~0.5 ng/ml after 3 months of follow-up. (F) Case 6 had only 15 days of follow-up and (E) cTnI was not measured in case 5. Collectively, these data reveal a consistent and persistent discordance between cTnI and cTnT trajectories in patients with IM3OS. MG-ADL, myasthenia gravis-activity of daily living scale; CK, creatine kinase; cTnT, cardiac troponin T; cTnI, cardiac troponin I; IVIG, intravenous immunoglobulin; prednisone ED, prednisone equivalent dose; RTX, rituximab; IM3OS, myocarditis with myositis and/or myasthenia gravis overlap syndrome.

(cases 1, 2 and 4) had good prognoses without apparent sequelae, 1 (case 5) was bedridden, and 2 (cases 3 and 6) died. The detailed treatment process and prognosis are as follows:

Case 1 received intravenous methylprednisolone (IVMP) at 120 mg per day for the initial 3 days. Due to an increase in cTnI, the IVMP dose was increased to 240 mg per day and tapered every 3-4 days. This was followed by a tapering dose of oral prednisone (starting at 75 mg daily, tapering off 5 mg every week). After 1 month, most symptoms had disappeared, except for mild neck fatigue and ptosis (MG-ADL score 3). After discontinuing ICIs, the tumor state was stable.

In case 2, due to rapid disease progression, to avoid myasthenic crisis caused by high-dose steroids, upfront plasmapheresis was initiated, but it was prematurely interrupted

due to ST-T dynamic deviation and severe coronary artery stenosis, suggesting myocardial ischemia. IVMP (80 mg/day) was initiated for 2 weeks, followed by oral prednisone (starting at 60 mg daily and tapering off 5 mg every week). The patient's clinical symptoms resolved except for mild dysphagia and ptosis 2 months after discharge (MG-ADL score 4). However, the bladder tumor recurred, and the patient underwent bladder surgery. The patient ultimately succumbed to multiple metastases 3 years later.

In case 3, treatment with IVMP (80 mg/day) and IVIG (0.4 g/kg/day) for 7 days was initiated. However, the patient's condition rapidly deteriorated, leading to respiratory failure, which required non-invasive ventilation support. Consequently, the patient received a high dose of IVMP at 1,000 mg/day for 3 days, with a tapering dose of half every 3 days, followed by a tapering dose of IVMP 80 mg daily. Over the following days, the patient experienced gradual improvement in dyspnea, neck weakness and ptosis. The patient successfully weaned off the ventilator 1 month later, and the other symptoms slowly recovered (MG-ADL score 20). However, the patient succumbed due to pneumonia after 3 months.

In case 4, IVMP (60-80 mg/day) was initiated for 1 week, followed by oral prednisone (starting at 50 mg daily and tapering off 5 mg every week). The patient's clinical symptoms completely resolved except for mild ptosis 1 month after discharge (MG-ADL score 2). After discontinuing ICI use, the tumor state was stable.

Due to rectal cancer, to avoid the side effects of gastrointestinal bleeding, case 5 was treated with a combination of moderate-dose steroids and IVIG. Under ventilation support, the patient gradually recovered, and the ventilator was withdrawn. However, the rectal cancer relapsed and gastrointestinal bleeding occurred. The patient underwent rectal cancer surgery and 3 months later, he remained bedridden (MG-ADL score 15).

Due to rapid disease progression and a refusal to use a ventilator, case 6 succumbed despite being given high-dose steroids, IVIG and rituximab (last MG-ADL score 21).

Overall, 4 patients (cases 1, 2, 4 and 5) received low dose pyridostigmine bromide for symptomatic management, which was not well-tolerated in cases 1 and 2, resulting in bradycardia and markedly prolonged PR intervals. In case 1, a single dose of pyridostigmine bromide (30 mg) was administered but later discontinued due to an increase in the PR interval (from 240 to 260 msec) and a drop in the heart rate to 40 bpm. In case 2, pyridostigmine bromide (30 mg, three times per day) was also administered but later withdrawn due to dyspnea and a heart rate drop to 40 bpm. In cases 4 and 5, low dose pyridostigmine bromide (30 mg, twice per day) was also administered, and no adverse reactions were found. In cases 3 and 6, due to severe abnormal electrocardiogram readings, pyridostigmine bromide was not prescribed.

Discussion

In the present study, all the patients had elevated CK levels and met the probable ICIs-induced myositis diagnostic criteria. Among the 4 patients who underwent EMG, no fibrillation potentials, positive sharp waves or myopathic motor unit potentials were observed. This is likely due to the following reasons: i) The most susceptible muscles, such as the paramuscular muscles of the neck, were not tested; and ii) the interval between symptom onset and EMG testing was too short. Typically, it takes 2 to 3 weeks for abnormalities to be detectable on EMG, and the rapidly progressive nature of ICI-induced myositis may not always allow for a timely EMG evaluation (1). Notably, 2 patients in the present study exhibited myotonic discharge in the sternocleidomastoid muscle. Previous research has indicated that myotonic discharges have high specificity for disorders characterized by inflammation, necrosis, splitting or vacuolar changes (19). We therefore hypothesize that myotonic discharges may serve as an electrophysiological marker of irMyositis. Muscle pathology and muscle MRI are essential for confirming the irMyositis diagnosis (16), but these tests were not conducted in this group.

In all 6 cases, CK levels peaked early in the disease course and decreased rapidly after treatment, yet clinical symptoms persisted or worsened. For example, 1 case (case 3) had moderately elevated peak CK levels (2,517 U/l), but the clinical symptoms were severe, and the prognosis was poor (Fig. 2C). These observations suggest the following: i) Elevated CK can be used as an early diagnostic biomarker of irMyositis; ii) CK levels and clinical severity may differ, so the peak levels of CK cannot be used to predict the severity of the disease; and iii) the rate of CK decline cannot reflect the patient's response to treatment and prognosis.

All 6 cases met with the IC-OS ICI-induced myocarditis clinical diagnosis. ICI-mediated cardiotoxic effects are rare and potentially fatal (4,20). The severity of cardiotoxicity can range from asymptomatic laboratory abnormalities (for example, cardiac biomarker elevation or ECG changes) to fulminant myocarditis, cardiogenic shock, complete heart block, ventricular arrhythmias and cardiac arrest (4,20). The mortality rate of ICI-related myocarditis (irMyocarditis) ranges from 25 to 50% (21). The present patients had elevated myocardial enzyme levels, arrhythmia including prolonged PR interval, bradycardia and sinus tachycardia, which confirmed the diagnosis of irMyocarditis. Evidence of active myocardial inflammation on cardiac MRI, cardiac ^{18}F-fluorodeoxyglucose PET/CT and endomyocardial biopsy can be used to confirm an irMyocarditis diagnosis (4).

The present study revealed an intriguing phenomenon: Despite a marked decline in CK and cTnI following treatment, cTnT elevation persisted. The underlying mechanism for this discordant trajectory between cTnT and cTnI remains unclear. We propose three potential explanations: i) Elimination kinetics. Some studies have suggested that TnI has a shorter plasma half-life than TnT, so that TnT elevation might persist for a longer time (up to 60 days) beyond the healing of myocarditis (22). However, a recent study reported completely opposite findings, showing that the elimination half-life of cTnT (134.1 min) is shorter than that of cTnI (239.7 min) (23). Therefore, the persistent cTnT elevation observed in the present patients cannot be explained by slower clearance. ii) Assay variability. In the present study, cTnT was measured using the Roche Cobas e801 analyzer, whereas cTnI was measured using the Beckman Coulter UniCel DXI800 analyzer. Given that the between-method variation between cTnI and cTnT assays has been reported to reach 127% (24), assay variability cannot be excluded as a potential contributing

factor. iii) Skeletal muscle cross-reactivity of cTnT assays. As demonstrated by Schmid *et al* (25), in patients with skeletal muscle diseases without evidence of myocardial injury, cTnT levels are frequently elevated, whereas cTnI concentrations remain largely within normal limits. Ectopic TnT expression has been documented in both non-inflammatory myopathies and myositis, and regenerating skeletal muscle fibers have been shown to express TnT during the repair process (1,22,26). Thus, the persistent elevation of cTnT observed in the present patients may be attributable to ongoing skeletal muscle regeneration following muscle injury. Consequently, in the IM3OS population, where skeletal muscle injury is a dominant and persistent component, relying solely on cTnT for monitoring may lead to unnecessary prolongation of therapy, whereas cTnI-guided de-escalation may offer a more accurate reflection of myocardial injury resolution. Therefore, in patients with extensive skeletal muscle damage, such cross-reactivity may yield false-positive cTnT results, and cTnT measurements should be interpreted with caution in the setting of skeletal muscle disease (25). Given that myocarditis and myositis frequently co-occur as irAEs of ICIs, cTnI may serve as a more reliable cardiac-specific biomarker for both the diagnosis and monitoring of irMyocarditis (22). However, conflicting evidence exists. A previous study demonstrated that cTnT is associated with major adverse cardiomyotoxic events and is sensitive for the diagnosis and surveillance of ICI-related myocarditis (27). Therefore, whether cTnT or cTnI should be prioritized for the diagnosis and prognostication of irMyocarditis remains an open question that warrants further investigation in larger, prospective cohorts.

All 6 patients within the present study exhibited notable fatigable external ophthalmoplegia (bilateral ptosis with or without ocular motor dysfunction), a finding consistent with an MG-like presentation that raised clinical suspicion of coexisting MG. Positive results in the fatigue test and ice-pack test, and increased jitter in SF-EMG supported the diagnosis of MG; however, only 1 patient (case 5) met the probable irMG diagnostic criteria. The remaining 5 patients met all other criteria for possible irMG, with the sole exception of elevated CK. The low percentage (1/6) of MG diagnostic rate in this group is partly attributed to the low rate of MG antibody test completion (2/6). Previous studies have indicated that the clinical presentation of irMyositis can resemble that of irMG, and ocular motor dysfunction and/or ptosis with a dropped head may serve as distinctive clinical features of irMyositis (28). According to the diagnostic criteria, in patients with markedly elevated CK and no evidence of MG, irMyopathy should be considered (16). However, it is worth noting that patients with irMyositis typically do not report any fluctuations in muscle weakness (28). Recognizing the overlapping clinical features between irMyositis and irMG is crucial, as their treatments differ, yet distinguishing between the two entities remains challenging given their shared presentation (28). AChR antibody and RNS can also help differentiate irMG from irMyositis. However, the positivity rates of RNS and anti-AChR antibodies are lower. SF-EMG may have a potentially higher sensitivity in diagnosing irMG and differentiating irMG from irMyositis (1). However, SF-EMG is not included in the definition of irMG published by Guidon *et al* (16), which may partly explain the low MG diagnostic rate in this group. Additionally, jitters can be influenced by myositis, complicating its use as a definitive diagnostic indicator. In the future, it may be possible to explore the threshold value for jitters that differentiates myositis from MG.

Recognizing the frequent co-occurrence of myocarditis with myositis and/or myasthenia gravis, experts have introduced the term 'ICI-induced myocarditis with myositis and/or myasthenia gravis overlap syndrome' or 'IM3OS', which denotes the combination of ICI-associated myocarditis with either myositis, MG or both (6). By this definition, IM3OS may be applicable to diagnostically challenging cases with objective evidence of neuromuscular or muscle involvement, provided that definitive myocarditis is confirmed. The complete phenotype, encompassing all three conditions, is specifically termed triple M syndrome (29). However, the underlying mechanisms responsible for IM3OS remain unclear. Some theories suggest that molecular mimicry and the critical role of PD-1 signaling pathways in regulating autoimmune responses in these tissues might be contributing factors (6). Further research is needed to gain a better understanding of this complex syndrome and its underlying pathophysiology.

According to the literature, the median interval between ICI initiation and neurological irAE onset was 25 days (range, 5-87 days) (28). Consistently, the median time interval between initiating ICIs and disease onset in the present 6 patients was 30.50 days (range, 18-42 days). In addition, case 1 exhibited the earliest seeking of medical treatment and presented with the mildest clinical symptoms, whereas case 3 delayed seeking treatment and had the most severe clinical symptoms. These results indicated that early hospital admission and treatment seem to be linked to improved prognosis and decreased healthcare costs. However, both cases 5 and 6 were treated early and in a timely manner, but the prognoses were still poor, suggesting that for patients with rapid progression, much earlier and stronger treatments might be needed. Therefore, healthcare providers should implement intensive follow-up surveillance strategies after initiating ICI therapy.

Regarding treatment, the first step involves discontinuing ICIs, depending on the severity of the disease (4,30). In all patients within the present study, ICI therapy was discontinued immediately after the diagnosis of IM3OS. The second step entails administering corticosteroids, which should be considered as the first-line treatment and initiated early, even in settings where corticosteroids are not typically recommended (4,31). Some experts suggest using the high-dose steroids for ~2 weeks and then gradually tapering to the lowest effective maintenance dose over 1-2 months, given the potential adverse effects of high-dose glucocorticoids (31,32). Sometimes, second-line treatments, including plasmapheresis and IVIG, or potentially more potent immunosuppressive agents, such as mycophenolate mofetil, rituximab or infliximab, should be considered (4,30,31). However, the optimal timing for initiating these agents, as well as their selection and sequencing, has yet to be clearly defined (9). We suggest that IVIG or plasmapheresis should be initialed when the patient has rapidly progressive bulbar weakness and respiratory compromise. High-dose corticosteroids have been recommended for severe irMyosititis and irMyocarditis, but they should be used with caution in severe irMG due to

Table II. Summary of findings from previous IM3OS case series and literature reviews.

First author, year	Number of cases	Key findings	Mortality rate, %	(Refs.)
Pathak *et al*, 2021	60	IM3OS can be associated with marked mortality and morbidity.	60	(6)
Wai Siu *et al*, 2022	7	Importance of prompt comprehensive testing to confirm diagnosis, early involvement of multidisciplinary team and early initiation of treatment.	29	(9)
Longinow *et al*, 2023	11	Troponin, elevated creatinine and reduced hemoglobin are possible early biomarkers in deceased patients.	36	(7)
Lipe *et al*, 2021	7	Early recognition of the triad, airway support, administration of high-dose glucocorticoids and early involvement of a multidisciplinary team are life-saving interventions.	29	(8)
Weaver *et al*, 2023	10	Good outcomes associated with early intensive immuno-suppressive treatment with IVIG and IVMP.	10	(33)
Deharo *et al*, 2022	3	Early high-dose corticosteroids and targeted immuno-suppressive therapy are needed.	33	(34)

IM3OS, myocarditis with myositis and/or myasthenia gravis overlap syndrome; IVMP, intravenous methylprednisolone; IVIG, intravenous immunoglobulin.

the recognized risk of MG flare (1,30). When fluctuating oculobulbar weakness raises the suspicion for irMG, upfront IVIG or plasmapheresis should be considered for better outcomes (1). The present case series demonstrated that the clinical severity of IM3OS can range from mild symptoms to respiratory failure and death, and the disease progression rate was also different, so these findings indicate the significance of adopting an individualized treatment approach tailored to specific patient populations. Despite appropriate treatment, a high mortality rate of IM3OS has been reported in the literature at 10-60% (6-9,33,34) (Table II), and consistent with this, 2 out of 6 patients died of irAEs in the present study. The speed of disease progression, respiratory involvement, and early and timely blocking of the immune storm are related to prognosis. Recently, accumulating evidence has suggested that novel biological targeted therapies, such as efgartigimod [a neonatal Fc receptor (FcRn) antagonist], may act as promising rescue therapies for refractory ICI-induced IM3OS (35,36). Cobelas-Cartagena *et al* (35) reported a case of IM3OS in which the patient failed to respond adequately to conventional treatments, including IVMP, immunosuppressive agents, IVIG and plasmapheresis. Subsequently, the patient was treated with efgartigimod and achieved a notable, rapid and sustained clinical recovery (35). At the same time, emerging data indicate that eculizumab, a complement C5 inhibitor, has been employed as a rescue therapy for irMG, offering a rapid therapeutic alternative in refractory cases (37,38). While the present study cannot definitively establish that the 2 deceased patients (cases 3 and 6) would have benefited from these agents, the rapid therapeutic responses reported in the literature strongly suggest that eculizumab and efgartigimod may serve as promising salvage options when conventional treatment fails. Based on these recent therapeutic advances, we propose that novel biological targeted therapies, including complement inhibitors and FcRn blockers, hold potential for reducing both mortality and long-term disability in this life-threatening overlap syndrome. Nevertheless, further prospective studies are urgently needed to establish optimal treatment algorithms for this devastating condition.

Pyridostigmine bromide, a cholinesterase inhibitor, enhances neuromuscular junction transmission by reducing acetylcholine breakdown at cholinergic nerve terminals and is commonly used in the treatment of MG (39). In the present case series, however, pyridostigmine was poorly tolerated in cases 1 and 2. Both patients presented with pre-existing bradyarrhythmia secondary to irMyocarditis, and the addition of pyridostigmine markedly exacerbated their baseline conduction disturbances, a phenomenon that has not been previously reported. Clinically, severe bradycardia is uncommon in patients with primary MG without cardiac involvement, with only isolated case reports documented in the literature (40). By contrast, pyridostigmine-associated bradyarrhythmia was frequently observed in the present case series. We postulate that this heightened susceptibility is attributable to the autonomic effects of pyridostigmine. Specifically, enhanced parasympathetic activity may attenuate sinus node automaticity, thereby predisposing the patient to bradyarrhythmias (41,42). Notably, irMyocarditis itself is associated with a high incidence of conduction abnormalities, including complete atrioventricular block (25.4%), right bundle branch block (18.4%), ventricular tachycardia (13%) and sinus tachycardia (12%) (43). The cardiac effects of pyridostigmine present a 'double-edged sword'. While bradyarrhythmia is a well-recognized clinical risk, experimental evidence also suggests cardioprotective properties of pyridostigmine, such as attenuation of cardiac remodeling, improvement in cardiac and autonomic function, enhanced baroreflex sensitivity, better heart rate variability, reduced ventricular arrhythmias and protection against

ischemia-induced arrhythmias (42). Given the divergent effects of pyridostigmine, particular caution is warranted in patients with bradyarrhythmic irMyocarditis, as it may worsen pre-existing conduction disturbances.

The present study has some limitations. First, the small sample size (n=6) precludes meaningful comparisons across treatment modalities and limits the generalizability of the findings to the broader IM3OS population. Second, complete ancillary investigations, including muscle or myocardial biopsy, muscle MRI and comprehensive electrophysiological studies, were not available for some of the patients, largely due to the critical illness of the patients at presentation, which precluded safe and timely completion of these invasive or time-consuming procedures. Third, only 2 patients underwent MG antibody serological testing, as these tests were unavailable in the China-Japan Friendship Hospital, and the sample needed to be sent to other facilities for analysis. The remaining 4 patients declined to undergo testing at a different facility, resulting in a low MG diagnostic rate (1/6) within this group. Due to institutional constraints, definitive serological confirmation of MG was not available for most patients. However, the inclusion criteria were based on the presence of myocarditis with either myositis or MG, as captured by the 'and/or' in IM3OS, rather than on a definitive MG diagnosis. The overall classification of IM3OS therefore remains valid. Nevertheless, the proportion of cases with confirmed MG is likely underestimated in the present cohort, and the findings concerning the MG subtype should be interpreted with caution. Fourth, the symptoms of the 6 patients more closely resemble those of MG than myositis, which led to the use of the MG-ADL scale to assess disease severity and disease progression. However, one prominent symptom of IM3OS, namely a dropped head, was not included in the MG-ADL scale. Therefore, a new scale may need to be devised to more accurately assess the disease.

Despite these limitations, the present series provides valuable exploratory insights into the diagnosis and management of this rare and life-threatening condition. We strongly advocate for the establishment of prospective collaborative studies to systematically collect comprehensive clinical, serological and electrophysiological data, which are urgently needed to validate the present observations and establish evidence-based treatment algorithms for IM3OS.

In summary, the present study provides valuable insights and reference points for the diagnosis and treatment strategies of IM3OS. Serum cTnI, but not cTnT, can serve as a valuable marker of cardiac injury in patients with IM3OS. Early recognition and prompt treatment with corticosteroids and supportive care are crucial for improving outcomes in these patients. For severe cases that have rapidly progressive bulbar weakness and respiratory compromise, IVIG, plasmapheresis and/or high-dose methylprednisolone should be initiated as soon as possible to enhance the prognosis. Moreover, given the coexistence of myocarditis and MG in patients with IM3OS, caution should be exercised regarding the use of pyridostigmine. Given the high mortality and disability rates associated with IM3OS, novel biological targeted therapies, such as eculizumab and efgartigimod, may reduce fatal outcomes.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QS drafted the manuscript. WZ and RW contributed notably to editing the draft of the case report. QL, YL, QS and RW performed the diagnosis and administered the whole course of treatment in cases 1, 4 and 6. QS, WZ, YW, RW and DP performed the diagnosis and administered the whole course of treatment in case 2. JZ, HC and RW performed the diagnosis and administered the whole course of treatment in case 3. JM, QS and WZ performed the diagnosis and administered the whole course of treatment in case 5. All authors contributed to the article and approved the submitted version. All authors have read and approved the manuscript. QS, WZ and RW confirm the authenticity of all the raw data.

Ethics approval and consent to participate

The study was conducted in accordance with the Declaration of Helsinki and was approved by the Clinical Trial Ethics Committee of China-Japan Friendship Hospital (approval number: 2019-166-K115) on November 6, 2019, and written informed consent to participate was obtained from all patients or their legal guardians.

Patient consent for publication

Written informed consent was obtained from all patients or their legal guardians for the publication of this case series.

Competing interests

The authors declare that they have no competing interests.

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