Management of respiratory failure in immune checkpoint inhibitors-induced overlap syndrome: A case series

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Abstract

Purpose: To describe the diagnostic approach and management of respiratory failure secondary to the checkpoint inhibitor-induced overlap syndrome.

Methods: A retrospective case series of cancer patients receiving treatment with checkpoint inhibitors that developed overlap syndrome. All patients were admitted to the intensive care unit (ICU) at The University of Texas MD Anderson Cancer Center between August and October 2021.

Results: Four cases are described. In all the patients, a high troponinemia raised the concern for myocarditis, leading to a complete workup. However, the predominant feature of the syndrome differed among the cases. For instance, two patients showed marked myocarditis as the primary driver of disease with a shorter hospital stay, likely due to early recognition and treatment. In contrast, the other two patients had a prolonged need for ICU due to severe neuromuscular involvement secondary to myositis and myasthenia gravis. Treatment was based on steroids, plasmapheresis, intravenous immunoglobulin, and immunosuppressive biological agents such as rituximab and infliximab.

Conclusions: The management of respiratory failure is challenging, particularly in those patients with predominant myasthenia gravis. Along with intensive clinical monitoring, bedside pulmonary function tests can guide the decision-making process of selecting a respiratory support method, the timing of elective intubation, and extubation.

Introduction

The recent advent of immune checkpoint inhibitors (ICI) and immunotherapy have revolutionized the treatment of cancer. ICIs prevent solid and hematological malignancies from evading the natural antitumor response by targeting programmed cell death protein-1 (PD-1) receptor/ligand on T cells and cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4)[1]. Despite these advancements, ICIs can be associated with life-threatening immune-related adverse events such as overlap syndrome (OS) consisting of myasthenia gravis (MG), myositis, and myocarditis[2–4]. The most concerning is ICI-myocarditis, which is associated with a mortality rate of nearly 50% and other related cardiovascular events in up to 46% of cancer patients[5–8]. Contrarily, ICI-myositis has a mortality rate of approximately 21%, with half of patients having other severe co-morbidities and prolonged hospital stays[9]. ICI-myocarditis has an incident rate approaching 1%, with concurrent myositis between 30-40% and MG in up to 10%[10]. There is not a clear incidence rate for OS, in part possible due to under recognition and underreporting. However, several cases have been reported in small case series and case reports[2, 3, 7, 8, 11, 12]. Due to the high risk of multiple complications and high in-hospital mortality rates of 60% seen in OS[13], these patients require multidisciplinary management, usually in the intensive care unit (ICU). Here, we present a case series of four patients treated with ICI who developed OS and acute respiratory failure.

Methods

A retrospective case series of four consecutive critically ill cancer patients who developed ICI-induced OS. Patients were admitted to the ICU at The University of Texas MD Anderson Cancer Center August and October 2021.

Cases Descriptions

The Table 1 and figure 1 summarize the characteristics of the cases.

Table 1
Overlap syndrome cases characteristics

	Case 1	Case 2	Case 3	Case 4
Oncologic disease	Metastatic renal cell carcinoma	Metastatic prostate carcinoma	Metastatic squamous cell carcinoma	Adenocarcinoma of the lung
ICI	Nivolumab/Ipilimumab	Nivolumab/Ipilimumab	Cemiplimab	Nivolumab/Ipilimumab
Troponin T , Ref: <19 ng/L	620 ng/L	1383 ng/L	2,262 ng/L	565 ng/L
CK , Ref: <309 U/L	499 U/L	2,206 U/L	558 U/L	486 U/L
CK-MB , Ref: <10.5 ng/mL	61.2 ng/mL	116 ng/mL	62.6 ng/mL	131 ng/mL
Aldolase , Ref: <7.7 U/L	10.7 U/L	10.2 U/L	43.8 U/L	9.6 U/L
ECG	Sinus tachycardia without ischemic changes	New wide QRS morphology	Premature ventricular contractions	Significant for anterolateral ST depression
Echocardiogram	No wall motion abnormalities, LVEF 55%	No wall motion abnormalities, LVEF 63%	No wall motion abnormalities, LVEF 64%	Global hypokinesis, LVEF 40%
EMG	No neuromuscular junction dysfunction	Axonal and demyelinating motor and sensory peripheral neuropathy	Signs of myositis	Signs of myositis and Guillain-Barre syndrome
Heart catheterization	Singe vessel 60% stenosis	Multi vessel disease, 60% stenosis	Multi vessel disease, 60% stenosis	Deferred until stable
Myocardial biopsy	Leukocytes infiltration	Leukocytes infiltration	Leukocytes infiltration	Refused
Muscle biopsy	Leukocytes infiltration	Leukocytes infiltration	Not performed	Refused
ECG: Electrocardiogram. EMG: Electromyography. ICI: Immune checkpoint inhibitors. LVEF: Left ventricular ejection fraction. Ref: Reference normal level.				

Case 1

A 62-year-old male with metastatic renal clear cell carcinoma treated with four cycles of nivolumab (PD-1) and ipilimumab (CTLA-4) combination immunotherapy. The patient presented to the emergency department (ED) with dyspnea, tachycardia and weakness. The electrocardiogram (ECG) showed sinus tachycardia without ischemic changes. He had high troponin T (620 ng/L [Reference <19]), CK (499 U/L [Reference <309]), CK-MB (61.2 ng/mL

[Reference <10.5]), and aldolase (10.7 U/L [Reference <7.7]). He was placed on high flow oxygen therapy (HFOT) and was admitted to the ICU for suspected ICI-related overlap syndrome and received three pulse-dose steroids along with five sessions of plasmapheresis (PLEX). Transthoracic echocardiography showed a 55% left ventricular ejection fraction (LVEF) and no abnormal wall motion. Additional immunosuppression with rituximab was given. Coronary angiography revealed single vessel disease with a 60% stenosis of the left anterior descending artery, deemed non-contributory of the troponin T increase. Electromyography (EMG) showed subtle signs of myopathy with no apparent signs of neuromuscular junction dysfunction. Myocardial and quadriceps biopsies showed leukocyte infiltration consistent with ICI-related myocarditis and myositis. After clinical improvement, he was discharged home.

Case 2

A 76-year-old male with metastatic prostate cancer treated with nivolumab/ipilimumab. The patient had a history of coronary artery disease and a coronary bypass. He presented to the ED with dyspnea, productive cough, and fever for three days. He received empiric antibiotics for potential pneumonia. High troponin T (1,383 ng/L), CK (2,206 U/L), CK-MB (116 ng/mL), and aldolase (10.2 U/L) were found. ECG showed a new wide QRS morphology. An echocardiogram showed no signs of wall motion abnormality. However, given his prior cardiovascular history, he received aspirin, atorvastatin and was admitted to the ICU for concerns of overlap syndrome. Three days of pulse-dose steroids and five sessions of PLEX were given. During his ICU course, the patient developed muscle weakness, dysphagia, and dysphonia and required HFOT. Statins were held due to potential myositis. EMG suggested axonal and demyelinating motor and peripheral sensory neuropathy. Multivessel disease and 60% stenosis of the right coronary artery were found on cardiac catheterization. Endomyocardial and muscular biopsies confirmed myocarditis and myositis. As weakness and orthopnea continued despite high-dose steroids and PLEX, treatment with infliximab and rituximab was initiated. After 12 days in the hospital, the patient was discharged home with physical therapy.

Case 3

A 72-year-old male with metastatic squamous cell carcinoma of the groin presented to the ED, after his third cycle of cemiplimab (PD-1), with worsening lower extremities muscular weakness and dysphagia. The patient was admitted to the ward, and laboratory results found high troponin T (849 ng/L), CK (558 U/L), and aldolase (43.8 U/L), indicating a potential overlap syndrome. The EMG showed signs of myositis. Frequent premature ventricular contractions were reported in the ECG. Paraneoplastic and myasthenia gravis antibodies panel were negative. On day 12 of hospitalization, the patient was found unresponsive after he underwent a percutaneous endoscopic gastrostomy, required emergent intubation with subsequent invasive mechanical ventilation (IMV), and was transferred to the ICU. Despite pulse-dose steroids and PLEX, the troponins remained high. Additional treatment with intravenous immunoglobulin (IVIG), rituximab, and pyridostigmine was given. The cardiac biopsy was consistent with myocarditis. His ICU stay was characterized by profound muscular weakness prompting the need for a tracheostomy. The patient repeatedly failed breathing trials and was unable to liberate from the ventilator due to poor respiratory mechanics. After a month in the ICU, the patient was discharged to a long-term acute care facility.

Case 4

A 72-year old male with metastatic adenocarcinoma of the lung, treated with nivolumab/ipilimumab admitted to the hospital due to COVID-19 acute respiratory failure. During his hospitalization, oxygen requirements increased, the patient was intubated and admitted to the ICU. The patient developed viral sepsis and required vasopressor support. On day 10 in the COVID ICU, troponin T was elevated to 86 and then peaked slowly over a week to 565 ng/L. His CK was (486 U/L), CK-MB (131 ng/mL), LVEF 40%, and global hypokinesis were found on echocardiogram. ICI-myocarditis and ICI-myositis were suspected due to troponinemia and failure to wean from the ventilator, respectively.

The patient received two days of pulse-dose steroids and five sessions of PLEX, and a tracheostomy was placed. EMG showed a mixed pattern of myositis and Guillain-Barre syndrome. Given the critical illness and advanced cancer condition, the patient's family refused heart catheterization. Thus, based on the use of combination ICI, clinical course, and EMG findings, the medical team determined a presumed diagnosis of OS.

Discussion

We describe a case series of four patients with OS. OS can present with different clinical courses and a predominance of one or more of the components of the syndrome. This raises challenges in the diagnosis of OS; as there is no standard definition or criteria that can be met[1, 6]. Despite the broad range of clinical syndromes in OS, the therapies are convergent. One of the most challenging aspects is the management of acute respiratory failure; hence, this is the focus of our discussion. This is demonstrated in **Case 1** and **Case 2**, as they were initially admitted for myocarditis related arrhythmias, but had a high risk of impending respiratory failure.

The main indicator of potential immune-related adverse event is elevated troponin upon admission. Although troponin I is more clinically significant for ICI-myocarditis, troponin T can also be elevated in patients with concomitant ICI-myositis[14]. Since there was high clinical suspicion for OS, a subsequent diagnostic work-up was performed which included biomarkers as troponin T, CK-MB, CK, and aldolase, ECG to rule out ischemic changes, echocardiogram to rule out myocardial wall dysfunction, left heart catheterization to rule out obstructive coronary artery disease, cardiac biopsy to confirm myocarditis, and EMG and muscle biopsy to confirm myositis and MG. Patients were later admitted into the ICU for ICI-induced OS and received pulse-dose steroids and PLEX. More specifically, **Case 1** and **2** were treated empirically with pulse-dose steroids due to high clinical suspicion for OS, **Case 3** and **4** were treated once a diagnosis of OS was confirmed. Initial therapy response was measured and subsequently followed by trending troponin T and CK after starting pulse-dose steroids. Since there is no current standardized treatment protocol, all patients were further treated with PLEX, and additional immunosuppression. Of note, electromyography was not able to confirm neuromuscular junction changes consistent with ICI-induced MG. Given our small sample size, this is consistent with other case studies as ICI-induced MG is much more difficult to diagnose with only 57% of patients having clear electrodiagnostic features of MG (41%) or MG and myopathy (16%)[15]. Although, ICI-OS has a high mortality rate approaching 60%[13]; all of our patients were discharged home or to long-term facilities. This could be possibly due to early recognition and our aggressive treatment approach.

To identify efficacious treatment approaches towards ICI-induced MG, it is important to characterize the differences between ICI-induced MG and idiopathic MG (iMG). Cases of iMG typically have an insidious clinical course, taking 2-3 years to become to develop symptoms of neuromuscular respiratory failure (NMRF) requiring support with non-invasive ventilation (NIV) or IMV [16, 17]. However, patients with ICI-induced MG can progress to NMRF in a median time of 7 days[15], as demonstrated in **Case 3**. Therefore, ICI-induced MG is associated with worse clinical outcomes than with iMG, including a higher risk of respiratory paralysis and death[18]. ICI-MG is also increasingly difficult to diagnose, since there are lower positivity rates in electrodiagnostic testing and lower seropositivity of anti-AChR antibodies than there is in iMG[1]. These differences in presentation and diagnosis could also lead to differences in management. While corticosteroids are a standard of care (in conjunction with IVIG and PLEX) and lead to more favorable outcomes of ICI-induced MG in OS[15], corticosteroid use can increase the progression of respiratory failure in iMG[19].

Pulmonary function tests and arterial blood gas can be used as prognostic indicators in a variety of diseases, but their use NMRF in OS is poorly understood. Findings in early NMRF include hyperventilation with rapid/shallow breaths resulting in hypocapnia that progress in late NMRF to hypoventilation with hypercapnia. When PaCO₂ reaches

between 40-45 mmHg and pH < 7.35, this indicates respiratory failure. However, bedside pulmonary tests have been assessed to predict the need for respiratory support. In a study by Seneviratne and colleagues, arterial gases had poor predictive value of the duration and outcome of NIV or IMV in myasthenic crisis[20]. Contrarily, a systematic review showed that patients with a maximum expiratory pressure (MEP) > 40 cm H₂O, vital capacity (VC) > 20 mL/kg or maximum inspiratory pressure (MIP) < -40 cm H₂O typically do not need mechanical ventilation[21]. More specifically, a decline in 30% of the MIP predicted a higher risk of IMV or NIV in these patients[21].

Due to the fluctuating clinical course of NMRF in OS, symptom severity is not a reliable predictor of improvement and stability. Nonetheless, general principles should be used to treat the underlying neuromuscular disorder, use NIV in eligible patients, and IMV when necessary. While there is not much data regarding treatment of NMRF in OS, we can use this case series and myasthenic crisis as a reference to guide future management.

Bilevel positive airway pressure (BiPAP) is preferred in myasthenic crisis because it can model natural respiratory mechanics. Ventilatory failure due to respiratory fatigue is the predominant mechanism of NMRF. BiPAP allows for modifiable and continuous positive pressures that decreases the risk for both atelectasis and upper airway collapse[20]. The benefits of BiPAP are significant, as 20% of patients in myasthenic crisis can be supported solely by NIV[22]. Predictors of NIV success include an Acute Physiologic Assessment and Chronic Health Evaluation II score < 6, bicarbonate < 30 mEq/L, and absence of overt hypercapnia (pCO₂ > 50 mmHg strongly correlated with failure; p < 0.01)[23, 24]. Patients managed initially with NIV prior to intubation require a shorter duration of ventilator support in comparison to patients only managed with IMV (4 vs. 9 days)[20]. Furthermore, prolonged IMV increases the risk of atelectasis, lowers MEP and is a frequent cause of longer ICU stays due to ventilator-associated pneumonia (VAP) and other systemic complications[20]. A BiPAP trial before established hypercapnia can prevent prolonged ventilation and intubation[20].

If NIV fails to improve the patient's respiratory status, intubation will need to occur without delay. Nearly 66%-90% of patients in myasthenic crisis require IMV at the emergency department or after admission into the ICU[25, 26]. Some subjective indications for intubation in NMRF are decreased levels of consciousness, diaphragmatic fatigue, bilateral facial and bulbar weakness (dysarthria, dysphagia, impaired gag reflex, staccato speech)[27]. Furthermore, hemodynamic instability, dysautonomia, and a deteriorating clinical course are objective indications that warrant intubation[27]. After successful intubation, patient's ventilator settings and the degree of respiratory support is largely patient dependent[28]. Of note, neuromuscular blockers should be used cautiously with ICI-induced MG patients. This is because the anti-ACh-R antibodies reduce the amount of functional ACh-R available for neurotransmission. Hence, depolarizing agents become less potent, while non-depolarizing agents increase their potency[29].

Predictors for prolonged ventilation in NMRF are integral in guiding the proper timing of a tracheostomy. Thomas and colleagues used a pre-intubation bicarbonate > 30 mEq/L, peak VC on days 1-6 after intubation of 25 mL/kg, and age > 50 years old to assess for patients that required prolonged ventilation in myasthenic crisis beyond 2 weeks[25]. Another study proposed comparing the bedside pulmonary function tests from the day of intubation and day 12 after intubation[30]. The investigators created the pulmonary function score by summing the VC, MIP, and MEP. A ratio (intubation/day 12 from intubation) <1 was associated failure to liberate from the ventilation within three weeks[30]. Once the need for prolonged ventilation is established, it is important to consider whether early vs. late intervention of tracheostomy provides any benefits. Some studies have shown that early tracheostomy was beneficial and resulted in decreased incidence of VAP[31], decreased use of sedation[32], earlier ICU discharge[33], and lower mortality[33]. However, other studies found no difference in length of stay[34], or mortality[35]. These conflicting results call for large clinical trials to address this clinical dilemma.

After adequate respiratory and clinical improvement, weaning from IMV can occur. Generally, patients should have: few secretions, an adequate cough reflex, and tolerate minimal pressure support for four hours without showing symptoms of respiratory fatigue[36]. A VC greater than 10-15 mL/kg for at least 4 hours was necessary before extubation could be considered[28, 37, 38]. In addition to these objective measurements, evaluating for improvement in the strength and tone of neck flexors and accessory respiratory muscles are important[38]. After extubation, patients should be transitioned to NIV[22]. The best predictor of extubation success is an improvement in the MEP[22]. Contrarily, extubation failure is most commonly associated with weak cough, inadequate airway clearance, older age, atelectasis, pneumonia, acidosis, decreased VC, and the need for NIV[24, 39, 40]. Hence, in patients with clinical suspicion of difficulty extubating, a trial of extubation over a Cook catheter can be performed[41]. Despite this, re-intubation still occurs almost 25% of the time[39, 40]. In a retrospective study, the median time to re-intubation was 36 hours in patients with myasthenic crisis[39]. If re-intubation is imminent, tracheostomy placement can also be considered[40, 42]. Often times, a concomitant percutaneous gastrostomy tube can be added at the same time to allow for long-term enteral access with minimal complications[43].

Conclusion

Although myocarditis occurs in less than 1% of patients receiving ICIs, once it presents, the risk of developing associated myositis and MG is 40% and 10%, respectively. Therefore, in any patient with ICI-related myocarditis, OS should be suspected and thoroughly investigated. OS is clinically diverse and potentially fatal and requires a multidisciplinary assessment. While there is no consensus, treatment is based on steroids, plasmapheresis, IVIG, and immunosuppressive biological agents. The management of respiratory failure is challenging, particularly in those patients with predominant MG. Along with intensive clinical monitoring, bedside pulmonary function tests can guide the decision-making process of selecting a respiratory support method, the timing of elective intubation and extubation.

Declarations

Conflict of interest disclosure: The authors declare no conflict of interest directly applicable to this research.

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Availability of data and material: We have full control of the data and agree to allow the journal to review these data if requested.

Authors contributions: Drs. Cuenca, Hanmandlu, Wegner, Botdorf, Nates, and Reddy had full access to all of the data in the study and take responsibility for its integrity and the accuracy of the data analysis. Concept and design: Cuenca, Hanmandlu, Nates, Reddy. Acquisition, analysis, or interpretation of data: Cuenca, Hanmandlu. Drafting of the manuscript: Cuenca, Hanmandlu, Reddy. Critical revision of the manuscript for important intellectual content: All authors. Supervision: Nates, Tummala, Iliescu, Reddy.

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Figures

Figure 1

Trends of clinical and laboratory parameters by cases. A: Troponin T. B: Creatine kinase (CK) C: Partial pressure of CO₂ (PCO₂). D: Maximum inspiratory pressure (MIP). E: vital capacity (VC).

Figure 2

Algorithm for workup of immune checkpoint inhibitors-overlap syndrome. ICI: Immune checkpoint inhibitor. CP: Chest pain. SOB: Shortness of breath. ECG: Electrocardiogram. EMG: Electromyography ICI: Immune checkpoint inhibitors. LHC: Left heart catheterization. RHC: Right heart catheterization.