Immune Checkpoint Inhibitor-Associated Triple ‘M’ Overlap Syndrome: A Case Study

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Introduction

Immune checkpoint inhibitors (ICIs) are monoclonal antibodies that block inhibitory receptors on T cells, effectively "releasing the brakes" on the immune system to enhance its ability to recognize and destroy cancer cells. Ipilimumab targets CTLA-4 (cytotoxic T-lymphocyte-associated protein 4), promoting T-cell activation and proliferation. Nivolumab targets PD-1 (programmed death-1), a receptor that downregulates immune responses through interaction with PD-L1 and PD-L2—ligands often overexpressed by tumor cells to evade immune detection.

While both agents are effective individually, their combination has shown superior efficacy in treating advanced melanoma. However, this comes with increased toxicity: one study reported grade 3 or 4 adverse events in 55% of patients receiving combination therapy, compared to 27.3% with ipilimumab and 16.3% with nivolumab alone.

Hospital 1

A 75-year-old male with metastatic melanoma presented to hospital 1 via EMS with severe fatigue, generalized weakness, and two episodes of syncope two days after the second cycle of ipilimumab/nivolumab

- Telemetry indicated sick sinus syndrome,
- EKG showed ST depressions.
- Troponin level: over 4,000 ng/mL

He underwent emergency coronary catheterization which revealed no coronary obstruction, and a pacemaker was placed
He also underwent transthoracic echocardiogram showed a preserved ejection fraction (60-65%) and no wall abnormalities

Discharged home in stable condition

Hospital 2

The patient’s condition worsened after discharge and developed new-onset dyspnea and dysphagia

Presented to his primary oncologist for a third immunotherapy cycle but was emergently transferred to Hospital 2 for evaluation of suspected ICI myocarditis

He was treated with colchicine and moderate dose solumedrol initially for myocarditis

After three days of moderate dose solumedrol, he was initiated on high dose steroids 1g daily x3 days followed by 40 mg BID of solumedrol per recommendation of Moffitt primary oncologist.

The patient did not improve and was transferred to Moffitt Cancer Center for further management.

Moffitt Cancer Center

Clinical presentation: His wife reported he had been experiencing head lag, ptosis, and blurry vision for two weeks.

Physical exam: Ptosis, neck and UE weakness, shallow breathing with mild hypoxia, requiring 2L NC.

Given the constellation of symptoms suggestive of myasthenia gravis, an elevated CK consistent with myositis, and a confirmed diagnosis of myocarditis, there was strong clinical concern for Triple ‘M’ Overlap Syndrome (TMOS). Of note, the patient’s liver enzymes were significantly elevated which was concerning for a concomitant ICI-associated hepatitis.

High-dose IV steroids were continued and IVIG was initiated.

The patient’s condition continued to deteriorate, and he elected to go home on hospice, where he unfortunately passed away the following day.

Discussion

Myocarditis is the most common and most fatal cardiotoxicity associated with ICI therapy, often presenting with elevated troponins and arrhythmias. In rare but severe cases, myocarditis co-occurs with myositis and myasthenia gravis, forming a life-threatening syndrome known as triple “M” overlap syndrome (TMOS). MG in the context of ICI therapy often presents with ptosis, dyspnea, diplopia, and myalgia, and is associated with a significantly higher rate of respiratory failure than idiopathic MG.

MG severity is graded based on clinical features, with grade 2 indicating moderate weakness, and grades 3–4 characterized by respiratory muscle involvement, significant dysphagia, or rapidly progressive weakness. Diagnosis can be supported by serum antibody testing, but treatment should not be delayed while awaiting results. Management includes corticosteroids—low-dose prednisone should be administered for grade 2. High-dose steroids and IVIG should be utilized in grades 3 and 4, with escalation to rituximab in refractory cases. For myocarditis, high dose steroids are initiated regardless of grade.

While TMOS remains a rare diagnosis, it carries an estimated mortality rate of 40%. Risk factors for TMOS include advanced age and those receiving combination ICI therapy. There is also emerging evidence that TMOS may be associated with a higher incidence of immune-related hepatitis compared to the individual conditions alone.

Conclusion

This case highlights the importance of prompt recognition and treatment of immune-related adverse events (iRAEs), particularly TMOS, in cancer patients treated with ICIs. Early consultation with medical oncology, cardio-oncology, and neuro-oncology are essential to improving outcomes.

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