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Case Report
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Fulminant Myocarditis Secondary to Nivolumab and Ipilimumab Dual Checkpoint-Inhibitor Therapy: A Case Report on Immune Checkpoint Inhibitor Cardiotoxicity

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Abstract

This case report identifies patients undergoing treatment with immune checkpoint inhibitors as a growing population at risk of developing myocardial injury ranging the spectrum from mild myocarditis/pericarditis-type symptoms to, in this case, fulminant myocarditis with cardiogenic shock. We herein also call for both a standard approach for treatment and identification of immune-checkpoint inhibitor myocarditis, as well as highlight some novel therapeutic options that have recently been described and are ongoing in clinical trials.

Herein we describe an 80-year-old woman history of atrial fibrillation, hypertension, hyperlipidemia, and newly diagnosed metastatic renal cell carcinoma treated with nivolumab and ipilimumab who presents with acute onset of diarrhea, anorexia, and dyspnea found to be in isolated right ventricular cardiogenic shock given non-obstructive coronary disease. Interventions and diagnostics included prompt initiation of high-dose methylprednisolone, a left heart catheterization and angiography, right heart catheterization with endomyocardial biopsy, and multimodal imaging including CT scans and transthoracic echocardiograms.

The main take-away lessons from this case are to consider immune-checkpoint inhibitor therapy in a patient presenting with overt or frank signs of cardiopulmonary overload, to always rule out ischemic etiologies of typical angina and acute heart failure symptoms, and to highlight standard and novel therapies for immune-checkpoint inhibitor-related cardiotoxicity.

Keywords: Case report; Checkpoint-Inhibitor; Myocarditis; Nivolumab; Ipilimumab; Renal cell carcinoma immunotherapy

Abbreviations

ICI: Immune Checkpoint Inhibitors; PD-1: Programmed Cell Death Protein 1; PD-L1: Programmed Death Ligand 1; RCC: Renal Cell Carcinoma; MSKCC: Memorial Sloan Kettering Cancer Center; ECOG: Eastern Cooperative Oncology Group; irAE: Immune-related Adverse Effect; ASCO: American Society of Clinical Oncology; EMB: Endomyocardial biopsy; SCAI: Society for Cardiovascular Angiography and Interventions

Introduction

Immune Checkpoint Inhibitors (ICI) targeting PD-1, PD-L1, and CTLA-4 have revolutionized care in numerous solid and hematologic malignancies [1-3]. Approximately 40% of patients with cancer in the United States were eligible for ICI treatment in 2019 [3]. ICI therapy has risen to become first-line therapy for Renal Cell Carcinoma (RCC). Recent trial data from the CheckMate-214 trial of untreated metastatic RCC showed that blockade of PD-1 and CTLA-4, with the monoclonal antibodies nivolumab and ipilimumab was superior to the prior standard of care with the tyrosine

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kinase inhibitor sunitinib [1,4].

ICI agents block the inhibitory signaling cascade that tumors utilize to evade cytotoxic T-cell targeting [3]. However, these agents function through non-specific checkpoint inhibition [5,6]. ICI therapy thus presents itself as a risk factor for nonspecific immune cell activation against various organ systems. We herein describe a case of isolated right ventricular cardiogenic shock due to fulminant myocarditis in the setting of nivolumab and ipilimumab therapy.

Case Presentation

An 80-year-old woman with atrial fibrillation, hypertension, and hyperlipidemia was diagnosed with clear cell renal cell carcinoma in 2013 (MSKCC prognostic score 1, ECOG 1), at which time she underwent right radical nephrectomy. In July of 2021, she was found to have disease recurrence and metastasis by paratracheal lymph node biopsy. A combination of nivolumab 270 mg plus ipilimumab 1 mg/kg was started every 3 weeks intravenous administered in a local community oncology infusion center.

Two weeks following cycle 4 and one day prior to admission, she experienced acute onset of profuse watery black stools, anorexia, and dyspnea. She was advised by her oncologist to be evaluated and presented to a community emergency department. Her physical exam at the time was significant for an ill-appearing woman with tachypnea, bibasilar crackles, tachycardia, with slight pitting edema bilaterally. In the emergency department, an EKG showed ST segment elevations in the inferior and lateral leads (Figure 1). She was given aspirin 325 mg, ticagrelor 180 mg, and started on a heparin drip prior to being transferred to our tertiary care facility for intervention. High-sensitivity troponin was elevated to 31,369 ng/L on arrival. She was COVID-19 negative by PCR and received the second dose of the Pfizer mRNA vaccine four months prior.

Coronary angiography demonstrated non-obstructive coronary disease, mild apical hypokinesis by ventriculography, and a left ventricular end-diastolic pressure of 18 mmHg. Shortly after the procedure, she became tachypneic, tachycardic, and hypoxic. Repeat EKG showed low voltage with diffuse ST segment elevations, and bedside echocardiography showed severe right ventricle dysfunction with low-normal left ventricular function (ejection fraction 50% to 55%). A CT chest/abdomen/pelvis with and without contrast was not suggestive of an obstructive, distributive, or hypovolemic etiology of her decompensation. She developed shock as evident by cardiac index of 1.5 L/min/m^2 and lactate of 4.2 units. The right atrial pressure was 17 mmHg and her pulmonary arterial pulsatility index was 0.88. She was started on dobutamine initially, and then escalating doses of norepinephrine and vasopressin. She went into an episode of ventricular tachycardia, received direct current cardioversion, amiodarone, and was intubated for airway protection.

Given the timing of her dual-checkpoint therapy two weeks prior, methylprednisolone was started at 1 gram IV daily for presumed immune-checkpoint inhibitor-mediated myocarditis. An Endomyocardial Biopsy (EMB) was performed, however, over the next 24 h, her hemodynamic instability worsened and per the patient's family and her prior expressed wishes; she was transitioned to comfort care and passed peacefully shortly thereafter.

The EMB showed myocardial tissue with diffuse interstitial lymphoplasmacytic infiltrates consistent with myocarditis (Figure 2). No giant cells were seen, and a Congo red stain was negative for Amyloid. Based on the MD Anderson grading and scoring system, her EMB was consistent with Grade 2 myocardial inflammation (definite myocarditis by Dallas Criteria) [7]. Immunohistochemistry was not performed on the EMB samples to further characterize the immunophenotypes of the infiltrating cells given the clinical course. Typically, positive staining for CD3, CD4, and CD8 T-cells with absent CD20 confirms the diagnosis of autoimmune myocarditis [7,8].

Discussion

This patient presented with rapidly progressive right ventricular predominant SCAI stage D cardiogenic shock. Given her coronary artery disease risk factors (age, hypertension, hyperlipidemia, atrial fibrillation), an ischemic cause was excluded by coronary angiography. Obstructive etiologies were ruled out by CT angiogram of her pulmonary arteries and serial echocardiograms for tamponade. Distributive shock was not consistent with a slightly elevated systemic vascular resistance of 16 Wood Units (1297 Dynes*sec*cm^3). Hypovolemic shock was ruled out by history/exam/imaging/labs.

Angiographic evidence from her LHC and serial TTE's pointed towards isolated right ventricular shock. To formally diagnose ICI-

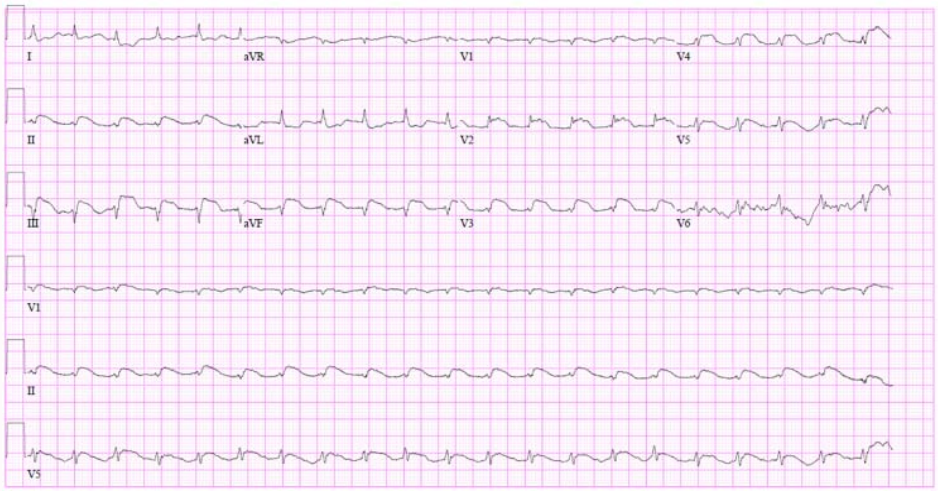

Figure 1: Admission EKG. Admission EKG showing low voltage with inferior and anterior/anterolateral ST segment elevations with reciprocal ST segment depressions in the high-lateral leads.

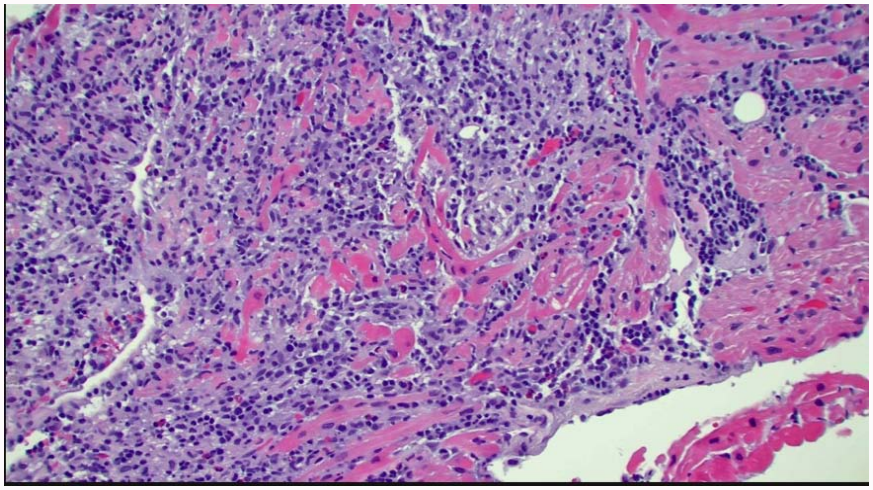

Figure 2: Endomyocardial Biopsy. Endomyocardial biopsy showing diffuse lymphoplasmacytic infiltration consistent with myocarditis (Grade 2 by MD Anderson, definite by Dallas Criteria). No giant cells and Congo Red stain was negative for Amyloid.

related myocarditis in this case, cardiac MRI *vs.* endomyocardial biopsy were the two options moving forward [5,6]. EMB is noted to be the more sensitive modality [5,6].

While overall rare, case reports and multicenter analyses have captured the increasing prevalence of cardiac immune-related adverse effects in the setting of increased use of immune-checkpoint inhibitors. Mahmood et al. found that the prevalence of myocarditis in a multicenter observational study was 1.14% (from 964 patients treated with ICI) [9]. Combination ipilimumab and nivolumab therapy are associated with a higher risk of developing myocarditis as opposed to single agent ICI [9].

From a treatment perspective, methylprednisolone was started at 1 gram per day given the high suspicion for ICI-myocarditis [6]. Other agents used in steroid refractory ICI-related myocarditis include IVIG [10], mycophenolate mofetil [11], infliximab [10], abatacept [11], and anti-thymocyte globulin [8]. All immunosuppressive therapies have been reported in single case reports or small case series, often extrapolating from other populations such as use of anti-thymocyte globulin in the treatment of heart transplant rejection [8], or tailoring strategies to immunophenotype (e.g. by serial measurements of circulating CD86+ monocytes in serum)to determine optimal dosing of abatacept and ruxolitinib [8,12].

As a result of increasing prevalence and identification of ICI-myocarditis, two recurring themes have emerged in the literature. The first is the question of optimal timing of glucocorticoid initiation. In many instances arriving at a definitive diagnosis of ICI-myocarditis requires substantial time and or clinical stability to obtain testing. However, given the rapid nature of myocyte infiltration and destruction, in patients with hemodynamic instability, high doses of steroids have been recommended. This is supported by a report from Zhang et al. indicating an association between higher initial corticosteroid dose, such as intravenous methylprednisolone 1000 mg daily, and earlier steroid initiation, with improved cardiac outcomes [13].

The second recurring theme is the call for more evidence and research aimed at developing treatment options for steroid-refractory and steroid-naïve ICI-myocarditis. As above mentioned, numerous immunosuppressive agents have been described with recent interest focusing on the anti-CD80/86 molecule abatacept (inhibiting activation of T-cells by blocking CD28 interaction). The Abatacept in Immune Checkpoint Inhibitor Myocarditis (ATRIUM, NCT05335928) trial is a new prospective double-blind clinical trial comparing the incidence of major adverse cardiac events between ICI-myocarditis patients on glucocorticoids treated with abatacept *vs.* placebo. A recent study of peripheral blood samples of patients with irAE correlated with PD-1 deficient mice with spontaneous myocarditis has identified a specific clonal subtype of cytotoxic Temra CD8+ cells with unique transcriptional changes that have further identified potential intervenable targets (such as chemokines CCL4/CCL4/CCL4L2) [14].

In summary, here we report a case of rapidly progressive dual ICI (nivolumab and ipilimumab)-related fulminant myocarditis presenting in cardiogenic shock with diffuse ST segment elevations, elevated troponin and diffuse lymphoplasmacytic infiltrates on endomyocardial biopsy. While our patient only received glucocorticoid therapy, there is growing evidence for novel immunosuppressive therapies and a continued focus on optimal treatment modalities for steroid-refractory as well as steroid-naïve ICI myocarditis.

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