possible precipitation of acute coronary syndrome with immune checkpoint blockade: a case report

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abstract

introduction: immune checkpoint inhibitors (ici) have led to improved survival in patients with a number of different tumor types. the ici agent nivolumab induces anti-tumor immune responses by inhibiting the programmed cell death 1 protein, but side effects include cardiac immune-related adverse events (irae) such as myocarditis.1 the association of nivolumab with atherosclerotic disease has been rarely reported.

case presentation: a 62-year-old man with metastatic melanoma and recent myocardial infarction (mi) presented with recurrent mi after having undergone several cycles of nivolumab therapy. repeat cardiac catheterization revealed rapidly progressive in-stent restenosis and diffuse coronary artery disease (cad) requiring bypass surgery and warranting cessation of nivolumab therapy.

conclusion: nivolumab has been linked with dysregulation of immune responses including enhanced t cell activity, which is implicated in cad. the timing of nivolumab therapy and presentation with non st elevation myocardial infarction in this patient suggests a serious t cell-driven medication adverse effect. therefore, close monitoring for atherosclerotic disease progression is warranted in patients on immunotherapy.

introduction

the recent use of immunotherapy agents such as immune checkpoint inhibitors (icis) in patients with advanced cancers has improved outcomes associated with several tumor types.1 these agents suppress tumor growth by inducing dis-inhibition of tumor specific immune responses. the anti-programmed death 1 (pd-1) antibody nivolumab has shown a significant survival benefit in comparison to standard therapy in patients with untreated metastatic melanoma.1 however, there have been accounts in the literature of several ici-associated immune-related adverse events (irae) including hepatitis, colitis, dermatitis, pneumonitis, and endocrinopathy.2 records of ici therapy-related adverse cardiovascular events in the literature primarily comprise cases of autoimmune myocarditis, pericarditis, and conduction disease.3,4 here, we report a case of rapidly progressive in-stent restenosis (isr) and severe worsening of coronary artery disease (cad) in a patient with metastatic melanoma started on nivolumab (table 1).

case presentation

a 62-year-old man with a history of metastatic melanoma and st elevation myocardial infarction (stemi) 4 months earlier treated with stenting (figure 1) presented to the emergency department with substernal chest pain. approximately 1 week prior to the current presentation, he had completed cycle 4 of ici therapy with nivolumab for metastatic melanoma. the patient had been diagnosed with stage iiic melanoma of the scalp 3 months ago. at the time of diagnosis, pet scan demonstrated right level v metastatic adenopathy, and brain mri revealed a 3 mm enhancing focus in the right parietal lobe suggestive of metastases. promptly after diagnosis, the patient underwent a right posterior scalp wide excision of the melanoma (breslow thickness 16 mm, pathologic stage pT4b N3b Mx). sentinel lymph node dissection at right neck level 5 identified melanoma in 4 out of 11 lymph nodes examined. the biopsied tissue was negative for mutations in codon 600 of the braf gene using pcr analysis. the patient was initiated on nivolumab therapy at 3 mg/kg every 2 weeks for 1 year. approximately 1 month prior to the cancer diagnosis, the patient had experienced the first mi, which was treated with percutaneous coronary intervention (pci) with two non-bifurcation drug eluting stents delivered to the middle left anterior descending coronary artery (lad) (2.5 mm × 16 mm) and first diagonal coronary artery (d1) (2.6 mm × 16 mm). interval echocardiography showed an improvement of ejection fraction from 45% to 55% while on aspirin, clopidogrel, metoprolol, atorvastatin, and lisinopril.

the patient's cardiac risk factors included a history of diabetes mellitus type 2 with a recent glycated hemoglobin percentage of 7.9%.

on admission, the patient was afebrile, normotensive, and without signs of dyspnea, lower extremity edema, or elevated jugular venous pulsation. initial electrocardiogram demonstrated sinus tachycardia and new st depressions in the anterior and anterolateral leads. initial troponin was 4.04 ng/ml, and serum bnp was 229 pg/ml (normal reference <300 pg/ml). a diagnosis of non st elevation
myocardial infarction (NSTEMI) was made for which the patient was heparinized and taken to cardiac catheterization, which showed significant changes in the degree of coronary stenosis from prior (Table 2). The findings were remarkable for ISR of the previously revascularized mid LAD and D1 (Figure 2), de novo significant occlusion of the ramus intermedius coronary artery, and interval worsening of stenosis of the left main coronary artery (LM), proximal LAD, and right coronary artery (RCA). Echocardiography demonstrated a depressed ejection fraction to 49% and extensive wall motion abnormalities diffusely throughout the myocardium. Given the recent use of nivolumab and cardiac catheterization findings, the diagnosis of immunotherapy-related atherosclerotic cardiovascular disease was strongly considered, and nivolumab was stopped indefinitely. Due to ISR and advanced multi-vessel CAD, the patient underwent coronary artery bypass grafting (CABG) with revascularization of the LAD, D1, RI, and RCA involving internal mammary artery to distal LAD and saphenous vein grafts to D1, RI. No other cancer-specific therapy was initiated at the time of discharge.

**DISCUSSION**

Cardiac adverse events associated with cancer treatment have become an increasingly salient issue given the advent of novel therapeutic agents with unique mechanisms of action. In the case above, we described an instance of rapidly progressive atherosclerotic disease, conceivably potentiated by ICI therapy with nivolumab. This agent has been reported to cause toxicities in 7% to 12% of patients receiving single agent therapy.1 Although there have been previously reported cases of myocarditis, pericarditis, and heart block associated with ICIs, cases of atherosclerotic disease and acute coronary syndromes (ACS) have been less frequently documented.5–7 While cancer patients have increased incidences of CAD and ISR8,9, and traditional risk factors such as diabetes, bifurcation disease, and stent characteristics may have contributed to the restenotic process, the rapidity of progression here is remarkable. Currently, the 1-year restenosis rates with contemporary stents in a real world setting are in the range of 1%.10 Even accounting for the patient’s risk factors, a progression from LAD intervention to multivessel disease requiring CABG in 4 months suggests the possibility of ICI induced cardiotoxicity as a mechanism of disease.

When bound to its ligands programmed cell death ligand 1 and 2 (PD-L1/2), PD-1 is responsible for abrogating T cell proliferation and cytokine production, thereby preventing destructive immune activation. This receptor is expressed on tumor-infiltrating lymphocytes in several types of cancers and its chronic activation by tumor antigens leads to anergy. Therefore, blockade of PD-1 is postulated to reverse this anergy and increase anti-tumor immune responses.5,6
Possible Precipitation of Acute Coronary Syndrome with Immune Checkpoint Blockade: A Case Report

Generally, toxicity from PD-1 inhibitors is precipitated by the dysregulation of immune responses that provokes pro-inflammatory and autoimmune-like syndromes. These syndromes are typically T cell-mediated, which is corroborated by histopathological examination of myocardium from patients with ICI-related myocarditis showing substantial T cell and macrophage infiltration. Recent literature suggests infiltrating T lymphocytes express T cell receptors against shared common antigens across tumor cells and myocardial cells, which likely contributes to myocardial injury. Additionally, PD-L1 is highly expressed on injured cardiomyocytes, positing a role for defective PD-1/PD-L1 signaling within myocardial tissue in this process.

It is well recognized that CAD is an inflammatory disease mediated by many of the same immune mechanisms implicated in T cell-mediated myocarditis. Atheroma on arterial intima are comprised of lipid-laden cells such as macrophages in conjunction with CD4+, CD8+, and natural killer T cells. These lesions are prone to rupture due to weakening from inflammatory cytokines and proteolytic enzymes secreted from the activated T cells, which may lead to ACS. Previous studies using murine models demonstrated a potential association of deficient or blocked PD-1 signaling with pro-atherogenic T cell responses. Bu et al. showed that mice deficient in PD-1 that were fed a cholesterol diet developed larger atherosclerotic lesions that contained more activated CD4+ and CD8+ T cells and macrophages compared to control mice. The CD4+ and CD8+ T cells in these mice were found to have increased expression of pro-inflammatory cytokine and chemokine receptor genes suggesting that these cells may be more competent at migrating to inflammatory sites such as atheromata and producing pro-atherogenic cytokines (i.e., Ifng and Tnf) compared to wild-type T cells. Furthermore, mice with PD-L1-deficient bone marrow had increased lesional inflammation compared to controls. Because PD-L1 is expressed in both hematopoietic and endothelial cells, deficient PD-1/PD-L1 signaling on T lymphocytes as well as within coronary vascular endothelium may contribute to CAD progression. Despite these findings, there have also been reports in the literature of nivolumab therapy associated with shrinkage of atheromatous plaques. This controversy emphasizes the point that causality cannot be determined from a limited number of cases and that further investigation is required to explore the role of PD-1/PD-L1/2 interactions in CAD.

It is also important to note that ISR is classified as a separate phenomenon to atherosclerosis. ISR is largely a result of neointima formation, which is characterized by smooth muscle cell (SMC) proliferation and migration and excessive extracellular matrix production. The patient in this case displayed several risk factors for ISR, including diabetes, large stent diameters, and ostial stenosis. However, systemic inflammation and immune dysregulation from ICI therapy may be possible contributors. Prior literature suggests that intimal inflammation and lymphocytic infiltration are determinants of in-stent neointimal growth. Additionally, studies have demonstrated that inflammatory cytokines stimulate the proliferation of vascular SMC, thereby leading to intimal thickening. Further research is warranted to study the direct effects of immune checkpoint inhibition on the restenosis process.

**CONCLUSION**

Reported here is the rapid progression of CAD and ISR as potential adverse effects of anti-PD-1 therapy. Despite its efficacy in cancer patients, ICI therapy is associated with various irAEs, a number of which are cardiovascular with high risk for mortality. For patients with established

<table>
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<th>Coronary vessel</th>
<th>Percent stenosis on initial catheterization after PCI</th>
<th>Percent stenosis on repeat catheterization 4 months later</th>
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<tbody>
<tr>
<td>Left main</td>
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<tr>
<td>Ostial/proximal left anterior descending</td>
<td>30</td>
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<tr>
<td>Mid-distal left anterior descending</td>
<td>0 (stented)</td>
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<tr>
<td>Ramus intermedius</td>
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<td>100 (de novo)</td>
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<tr>
<td>Right coronary</td>
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Possible Precipitation of Acute Coronary Syndrome with Immune Checkpoint Blockade: A Case Report

atherosclerotic disease initiated on immunotherapy, active surveillance for disease progression may be warranted. Measurement of serial troponins has been proposed as surveillance for myocarditis and may have utility for CAD as well.\(^5\) Additionally, multi-disciplinary discussion with patient participation should take place when confronting competing risks of metastatic cancer and ACS. Although the decision was made to cease ICI therapy in this case, the approach should be individualized for each patient. Lastly, further research is required to evaluate the role for early cardiac risk stratification, aggressive lifestyle modification, and optimization of cardioprotective therapies for at-risk patients on ICIs.

Disclosure Statement

The author(s) have no conflicts of interest to disclose.

Authors’ Contributions

RM conducted the literature review and wrote the manuscript with support from GM, RL, and KM. JT helped supervise the project.

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References