Introduction

While the cardiotoxicity associated with anthracycline chemotherapy is well-established, the cardiotoxicity associated with immune checkpoint inhibitors such as pembrolizumab has been described only in case reports and series. Here we report a case of pembrolizumab rapidly leading to fulminant heart failure and ultimately ventricular tachycardia.

Case

A 65-year-old female with history of recurrent metastatic endometrial carcinoma status post total abdominal hysterectomy and chemotherapy, with recent administration of second cycle of pembrolizumab presented with chest discomfort for two weeks. Prior to presentation, she experienced some shortness of breath following her first cycle of immunotherapy. After a CT angiogram was negative for pulmonary embolism, she was diagnosed with a COPD exacerbation, with slight improvement of her chest pain. She presented with recurrence of non-radiating chest pain, and was found to have a troponin of 12 with inferior EKG changes. She received nitroglycerin and was transferred to Maine Medical Center for further evaluation.

Notable Workup

- Elevated troponin of 4.0, trending up to 7.46
- Inferior ST elevations on presenting EKG
- Echocardiogram revealed significant systolic and diastolic dysfunction, ejection fraction 30%
- CT with angiogram was negative for pulmonary embolism
- Left cardiac catheterization demonstrated patent coronary arteries
- cMRI revealed late gadolinium enhancement involving the mid and apical septum, consistent with myocarditis

Hospital Course

- Started on 1 gm methylprednisolone daily
- On day four of admission, telemetry revealed atrial fibrillation with rapid ventricular response associated with hypotension. Wide complex tachycardia was captured on telemetry with persistent hypotension
- Echocardiogram revealed worsening ejection fraction of 10%
- Given her tenuous prognosis, made comfort measures only and expired
- Autopsy revealed diffuse lymphohistiocytic myocarditis with T cell mediated hypersensitivity indicative of pembrolizumab induced myocarditis

Notable Imaging

Figure 1. Cardiac MRI. Normal left ventricular cavity with moderate systolic dysfunction, slight increase in signal intensity on T2 weighting indicative of myocardial edema with late gadolinium enhancement of the mid and apical septum, consistent with myocarditis.

Pathology

A & B: Fixed heart sections showing hyperemia and fibrosis. B: H&E staining showing lymphohistiocytic myocarditis with multifocal areas necrosis and fibrosis. C: Immunostain with majority CD4+ subtype

Points on Immune Checkpoint Inhibitors

- Immune checkpoint inhibitors (ICI) are novel agents in advanced stage malignancies.
- Benefit in melanoma, metastatic renal cell cancer, and non small cell lung cancer.
- MOA: disruption of negative regulation of cancer cells’ ability to bind to receptors on circulating T cells.
- Cardiotoxicity manifestations: fulminant lymphocytic myocarditis, supraventricular and ventricular arrhythmias, pericardial disease, and Takotsubo-like cardiomyopathy.

- Underlying mechanism for toxicity is postulated to be due to aberrant activation of autoreactive T cells.
- Most likely with PD1 (pembrolizumab) or CTLA inhibitors, often 17-34 days after initiation of therapy.

Discussion

- Incidence of cardiotoxic event with ICIs is 0.09% in total, with about 0.5% experiencing an adverse cardiovascular event.
- Cardiotoxicity presents heterogeneously, as asymmetric elevation of cardiac biomarkers, nonspecific complaints of malaise, fulminant congestive heart failure and cardiogenic shock.
- In two reviews, almost 100% of patients had elevated cardiac biomarkers, 40 to 89% were found to have EKG changes, 79% were found to have changes on echocardiogram, and 50% with diminished ejection fraction (Yang 2018, Mahmood 2018).
- Histology may show patchy, gross T cell predominant lymphocytic infiltrate within the myocardium, similar to cardiac transplant rejection (Johnson 2016).
- Diagnosis requires a high degree of suspicion: Most cardiac MRI will not show late gadolinium enhancement or myocardial inflammation.
- Treatment consists of holding ICI and starting steroids, though treatment regimens vary. Other immunosuppressives have been tried in case reports.
- Adverse events following myocarditis are much more common than in the current literature: 50% of patients with ICI induced myocarditis experienced a major adverse cardiovascular event compared with 15% overall (Mahmood 2018).
- PD1 and CTLA inhibitors or a combination, are offenders in a disproportionate number of cases.

References


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