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Myocarditis in Patients Treated With Immune Checkpoint Inhibitors

Syed S. Mahmood, MD, MPH,[a,b] Michael G. Fradley, MD,[c] Justine V. Cohen, DO,[d] Anju Nohria, MD,[e] Kerry L. Reynolds, MD,[d] Lucie M. Heinzerling, MD, MPH,[f] Ryan J. Sullivan, MD,[d] Rongras Damrongwatanasuk, MD,[c] Carol L. Chen, MD,[g] Dipti Gupta, MD, MPH,[g] Michael C. Kirchberger, MD,[f] Magid Awadalla, MD,[b] Malek Z.O. Hassan, MD,[b] Javid J. Moslehi, MD,[h] Sachin P. Shah, MD,[i] Sarju Ganatra, MD,[i] Paaladinesh Thavendiranathan, MD,[j] Donald P. Lawrence, MD,[d] John D. Groarke, MB BCH, MPH,[e] Tomas G. Neilan, MD, MPH[b,k]

ABSTRACT

BACKGROUND Myocarditis is an uncommon, but potentially fatal, toxicity of immune checkpoint inhibitors (ICI). Myocarditis after ICI has not been well characterized.

OBJECTIVES The authors sought to understand the presentation and clinical course of ICI-associated myocarditis.

METHODS After observation of sporadic ICI-associated myocarditis cases, the authors created a multicenter registry with 8 sites. From November 2013 to July 2017, there were 35 patients with ICI-associated myocarditis, who were compared to a random sample of 105 ICI-treated patients without myocarditis. Covariates of interest were extracted from medical records including the occurrence of major adverse cardiac events (MACE), defined as the composite of cardiovascular death, cardiogenic shock, cardiac arrest, and hemodynamically significant complete heart block.

RESULTS The prevalence of myocarditis was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range 21 to 75). Cases were 65 $\pm$ 13 years of age, 29% were female, and 54% had no other immune-related side effects. Relative to controls, combination ICI (34% vs. 2%; $p < 0.001$) and diabetes (34% vs. 13%; $p = 0.01$) were more common in cases. Over 102 days (interquartile range 62 to 214) of median follow-up, 16 (46%) developed MACE; 38% of MACE occurred with normal ejection fraction. There was a 4-fold increased risk of MACE with troponin T of ≥1.5 ng/ml (hazard ratio 4.0; 95% confidence interval 1.5 to 10.9; $p = 0.003$). Steroids were administered in 89%, and lower steroids doses were associated with higher residual troponin and higher MACE rates.

CONCLUSIONS Myocarditis after ICI therapy may be more common than appreciated, occurs early after starting treatment, has a malignant course, and responds to higher steroid doses. (J Am Coll Cardiol 2018;■:■–■)
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From the [a]Cardiology Division, New York-Presbyterian Hospital, Weill Cornell Medical Center, New York, New York; [b]Cardiac MR PET CT Program, Department of Radiology, Massachusetts General Hospital, Boston, Massachusetts; [c]Cardio-Oncology Program, H. Lee Moffitt Cancer Center & Research Institute and University of South Florida Division of Cardiovascular Medicine, Tampa, Florida; [d]Division of Oncology and Hematology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts; [e]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts; [f]Department of Dermatology, University Hospital Erlangen, Friedrich-Alexander-University Erlangen-Nurnberg (FAU), Germany; [g]Cardiology Division, Memorial Sloan Kettering Cancer Center, Weill Cornell Medical College, New York, New York; [h]Cardio-Oncology Program, Vanderbilt University Medical Center, Nashville, Tennessee; [i]Cardiology Division, Lahey Hospital & Medical Center, Burlington, Massachusetts; [j]Ted Rogers Program in Cardiotoxicity Prevention, Peter Munk Cardiac Center, Division of Cardiology Toronto General Hospital, University of Toronto, Toronto, Ontario, Canada; and the [k]Cardio-Oncology Program, Division of Cardiology, Department of Medicine, Massachusetts General Hospital, Boston, Massachusetts. Dr. Mahmood has been supported by the Sarnoff Cardiovascular Research Foundation. Drs. Chen and Gupta are supported by National Institutes of Health (NIH)/National Cancer Institute (NCI) Cancer Center Support grant P30 CA008748. Dr. Thavendiranathan is supported by Canadian Institutes of Health Research New Investigator Award (FRN 147814). Dr. Neilan was supported in part through the Kohlberg Foundation, American Heart Association Fellow to Faculty Award 12FTF12060588, NIH/National Heart, Lung, and Blood Institute grants 1R01HL130539-01A1, 1R01HL137562-01A1, and K24HL113128-06, and NIH/Harvard Center for AIDS Research grant P30 AI060354. The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

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ABBREVIATIONS AND ACRONYMS

anti-CTLA4 = anti-cytotoxic T-lymphocyte-associated protein 4

anti-PD1 = anti-programmed cell death protein 1

anti-PDL1 = anti-programmed death-ligand 1

AUC = area under the curve

CHB = complete heart block

ECG = electrocardiogram

ICI = immune checkpoint inhibitor

LVEF = left ventricular ejection fraction

MACE = major adverse cardiac events

MRI = magnetic resonance imaging

Immune checkpoint inhibitors (ICI) represent a novel category of drugs that help direct the immune system to recognize and target cancer cells (1,2). The suppression of immune regulation is associated with immune-mediated adverse events. During initial regulatory approval in 2014, immune-mediated adverse events involving the neurological, endocrine, pulmonary, gastrointestinal, and renal systems were reported (3,4). Recently, in small case series, myocarditis was identified as a side effect of immune checkpoint inhibitors (5), but data on presentation, risk factors and outcomes are limited (6–9). At present, in the United States, there are almost 600,000 patients who may be eligible for ICI therapy (10), and the use of ICI is expected to increase significantly in the coming years (11). Hence, there is a need to better characterize ICI-associated myocarditis. After the observation of sporadic cases of ICI-associated myocarditis, we created a retrospective and prospective multicenter registry to provide data on 35 patients with myocarditis following ICI and compared them with contemporaneous ICI-treated patients who did not develop myocarditis; we detail the cardiovascular outcomes, as well as the presentation, treatment, and testing variables associated with those outcomes.

METHODS

PATIENTS. Cases were derived from an 8-center institutional registry (Online Table 1). The registry was formed in 2016 specifically designed for collating suspected cases of myocarditis related to ICI. The registry included both retrospective and prospective cases; the first case in the registry was from November 2013, and cases were included until July 2017. Controls were randomly derived from a single-center registry (Massachusetts General Hospital, Boston, Massachusetts) of all 964 patients started on ICI in the same time interval who did not develop clinical myocarditis. The number of patients treated with ICI therapy at Massachusetts General Hospital during the study period was confirmed by 2 independent researchers. Controls (3:1 ratio) were not pre-selected to match cases on any variables. To compare different types of steroids, the dose was converted to equivalent methylprednisolone units using standard conversion factors (12). The study was approved by each center's institutional review board, and the requirement for written informed consent was waived.

COVARIATES. Data on covariates of interest were extracted retrospectively from electronic medical records including standard demographics, cardiovascular risk factors, medications, electrocardiograms (ECGs), and echocardiographic variables. Admission troponin was defined as first measured serum troponin; peak troponin was maximum measured troponin; and discharge/final troponin was defined as troponin measured at discharge from index hospitalization or the troponin before an event if that event occurred on the index admission. Cancer-specific covariates included the type, ICI treatments, prior cardiotoxic chemotherapy, and prior radiation. Covariates specific to myocarditis also included clinical presentation, physical exam, coronary angiography (invasive or computed tomography) or stress testing, admission, peak and discharge cardiac biomarkers, and if available, cardiac magnetic resonance data, endomyocardial biopsy, and autopsy results, as well as treatments for myocarditis.

DEFINITIONS AND OUTCOME OF INTEREST. Myocarditis was diagnosed in 2 ways: 1) standard histological features present on endomyocardial biopsy or autopsy; and 2) a guideline-recommended scoring system for clinically suspected myocarditis that incorporates several variables including the clinical, biomarker and imaging features (13). Adverse event grading was performed using Common Toxicity Criteria for Adverse Events (version 4.0) (14). The outcome of interest, major adverse cardiac events (MACE), was a composite of cardiovascular death, cardiac arrest, cardiogenic shock, and hemodynamically significant complete heart block (CHB). In cases where cardiac arrest, cardiogenic shock, or CHB led to a death, that case was counted as a cardiac death. Standard definitions were used for cardiovascular

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