H51 Acute Myocarditis Following PD-1 Inhibitor (Nivolumab) Treatment for Lung Carcinoma

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Learning Overview: After attending this presentation, attendees will: (1) understand the pathophysiology of Immune Checkpoint Inhibitors (ICIs), (2) become aware of myocarditis as a severe immune-related adverse event. and (3) include immunomodulatory treatments in the differential diagnosis of acute myocarditis.

Impact on the Forensic Science Community: This presentation will impact the forensic science community by demonstrating the increasing need to include ICIs in the differential diagnosis of acute myocarditis when evaluating a patient's anticancer regimens.

Nivolumab is a monoclonal PDL-1 inhibitor in the class of ICIs used in the treatment of several malignancies, including non-small cell lung cancer, renal cancer, and melanoma.[1,3] Common reported treatment-related adverse events of immunomodulators include fatigue, decreased appetite, rash, diarrhea, and arthralgia, including treatment-related autoimmune effects in sites such as skin, kidney, lungs, brain, endocrine organs, gastrointestinal tract, and, more recently described, cardiovascular system.[1,2,4] Over-expression of inhibitory checkpoint molecules, such as Programmed cell Death Ligand 1 (PDL-1) allows cancer cells to prevent the body's natural immune response from activating CD8 T-cells, allowing the cancer cells to proliferate, escaping cytotoxic cell mediated death.[2] ICIs work by blocking PDL-1, which allows the CD8 T-cells to become active and kill cancer cells, although not without some notable side effects. Severe cases of immune-related adverse events have been well documented. Of these, approximately 0.06% to 0.27% of patients can experience immune-related myocarditis that can lead to arrhythmias, heart failure, and death due to cardiogenic shock.[2]

This presentation describes a fatal case of fulminant myocarditis after treatment with nivolumab in a 76-year-old man with metastatic lung adenocarcinoma. The patient presented with chest discomfort while at the infusion clinic; he reported experiencing some nausea and vomiting, shortness of breath, and dizziness approximately five days prior. Examination revealed atypical Electrocardiogram (EKG) findings, including ventricular tachycardia with apparent Atrioventricular (AV) dissociation and S-T segment elevations concerning for S-T-Elevation Myocardial Infarction (STEMI) with serum troponin elevations suggestive of a myocardial infarction; the patient died within one day of admission. Postmortem examination was requested by the clinical team with suspicion of metastasis to the AV node due to EKG findings.

At autopsy, the gross examination of the heart was unremarkable except for evidence of coronary atherosclerosis and focal pallor in the interventricular septum. Histologic examination revealed a fulminant myocarditis with infiltration of the myocardium by lymphocytes, numerous neutrophils and eosinophils associated with marked myocyte necrosis, and interspersed large atypical appearing cells. The large atypical cells were concerning for metastatic tumor; however, immunohistochemical workup ruled out carcinoma. Infective myocarditis workup performed at the Center for Disease Control could not identify a specific infectious etiology. Ruling out the presence of metastatic tumor and common infectious causes, the final diagnosis favored the immune check point inhibitor treatment as the etiology of the fulminant myocarditis.

Multiple immune checkpoint inhibitors are on the market for use in the anticancer regimens of a variety of cancer types, which has markedly increased the number of patients receiving these therapies. This report adds to the cases of acute myocarditis presenting after PD-1 inhibitor treatment and highlights the need to consider a broader differential in myocarditis presenting in patients with cancers treated by immunomodulators.

Reference(s):

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2. Johnson, D.B. et al. Fulminant Myocarditis With Combination Immune Checkpoint Blockade. *New England Journal of Medicine*, (2016): 375(18), 1749-1755. DOI: 10.1056/NEJMoa1609214.
3. Strauss, B.L. et al. Cardiac Metastases in Lung Cancer. *Chest*, Volume 71, Issue 5, May 1977, Pages 607-611, https://doi.org/10.1378/chest.71.5.607.
4. Semper, H. et al. Drug-Induced Myocarditis After Nivolumab Treatment in a Patient With PDL1-Negative Squamous Cell Carcinoma of the Lung. *Lung Cancer*, 99(2016) 117-119. http://dx.doi.org/10.1016/j.lungcan.2016.06.025.

Cardiac Pathology, Myocarditis, PD-1 Inhibitors