NYU Long Island School of Medicine

DEPARTMENT OF PATHOLOGY

Short Report in Pathology

Organ system: Pulmonary and Cardiovascular

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History:

We report a case of a 75-year-old female admitted to the emergency department after suffering from a ventricular fibrillation cardiac arrest at an outpatient office. Her symptoms warranted an admittance to the CICU where it was determined she had a myocarditis event, induced from an immune checkpoint inhibitor (Nivolumab) used to treat her existing stage III melanoma. In the CICU, the patient developed symptoms of myasthenia gravis (MG) including ptosis, hoarseness, and dysphagia, as well as respiratory distress. IVIG and steroids were started to treat the MG, but no improvement was noted. Patient ultimately succumbed to the MG.

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Gross Image:

None

Microscopic Images:

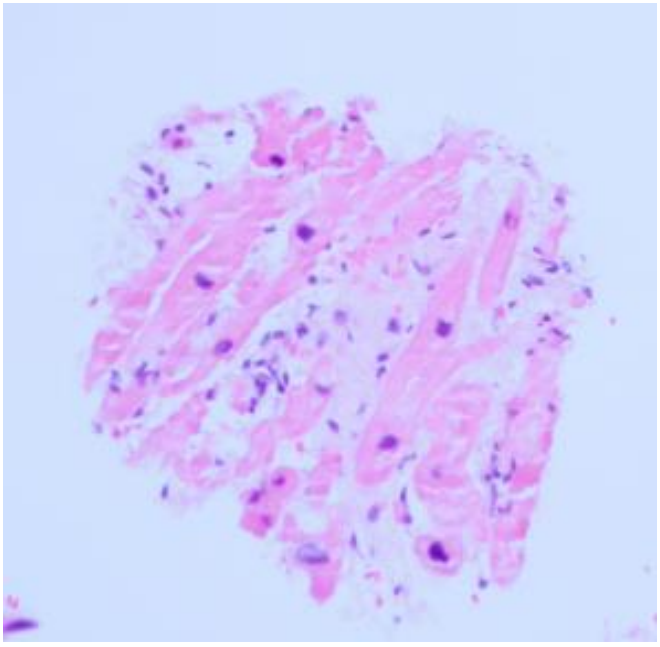

Figure 1: Myocardium with patchy infiltrate. (100x, H&E)

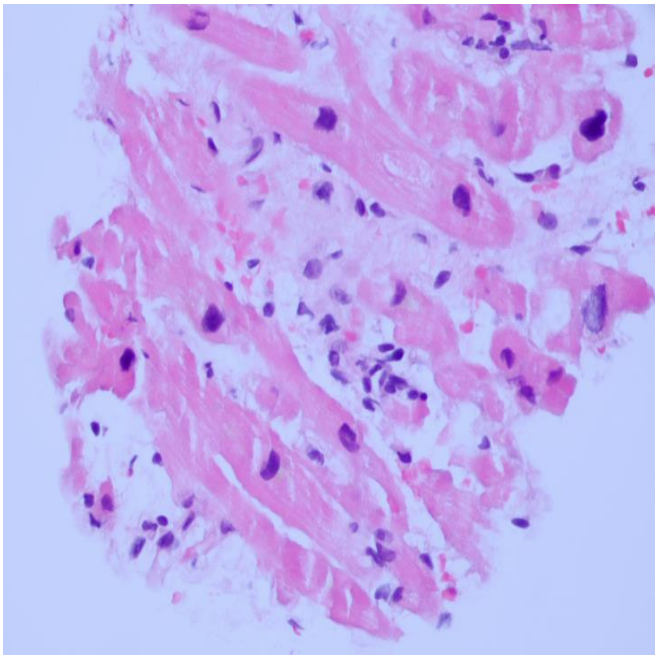

Figure 2: Myocardial infiltrate consists of scattered lymphocytes with separation of myofibers. (400x, H&E)

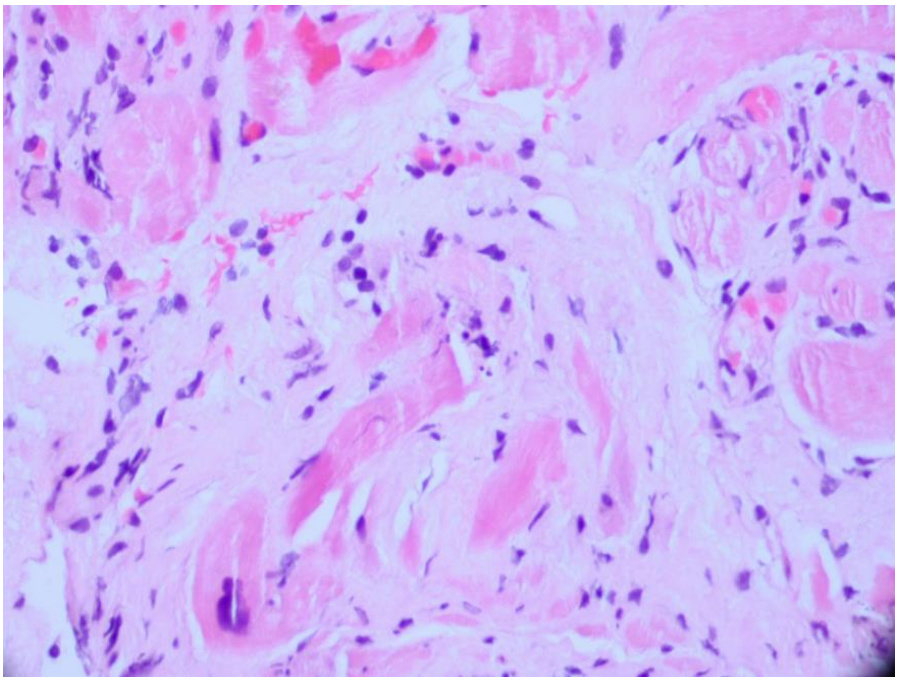

Figure 3: Damaged myocardial fibers with associated fibrosis and lymphocytes consistent with lymphocytic myocarditis. (400x, H&E)

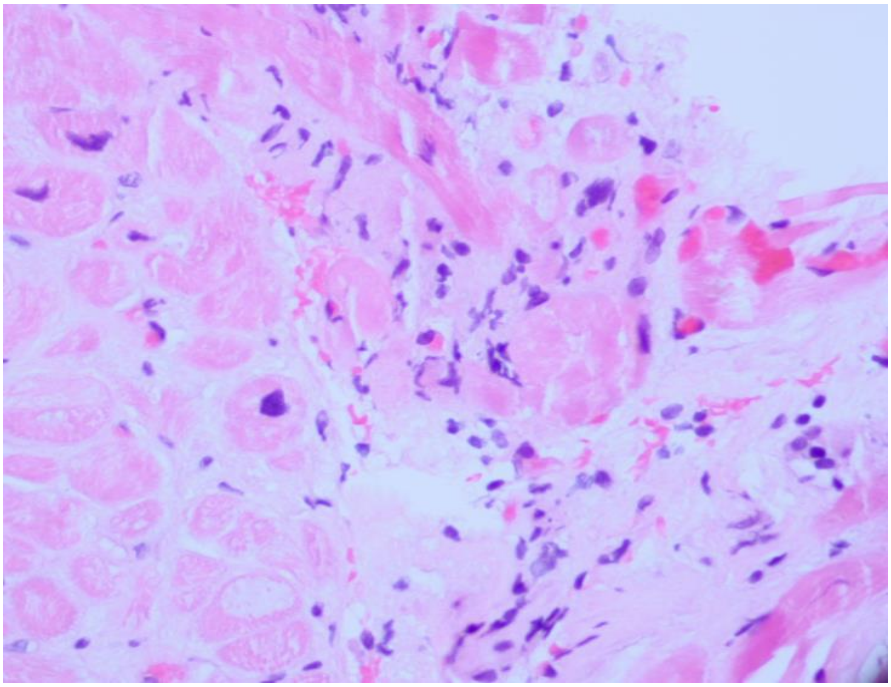

Figure 4: Aggregates of lymphocytes around myocardial fibers, consistent with myocarditis. (400x, H&E)

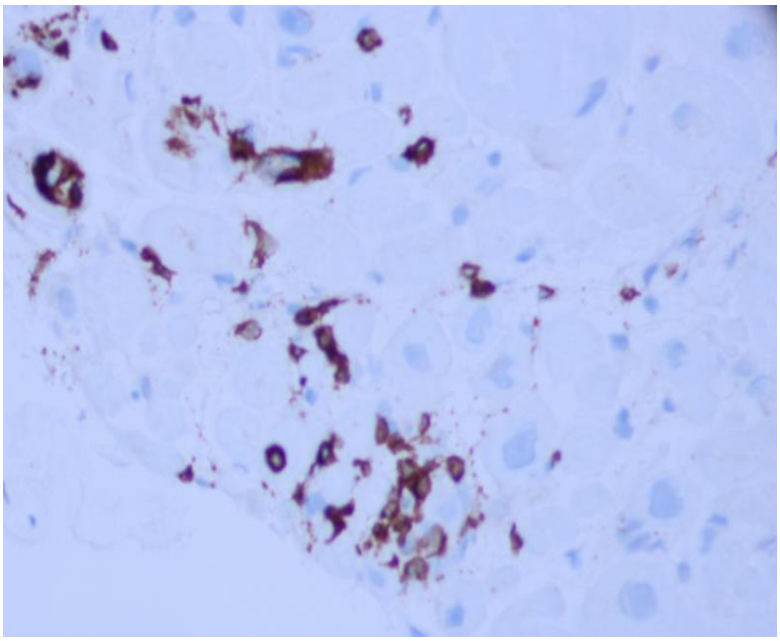

Figure 5: Immunoreactive infiltrate consistent with T-lymphocytic infiltrate. (400x, CD3 immunohistochemical staining)

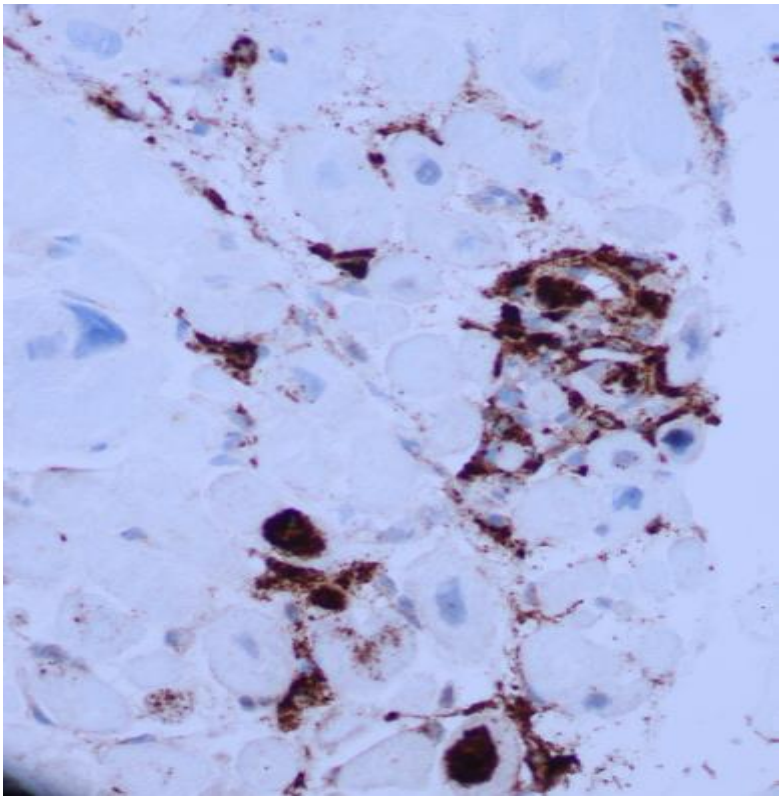

Figure 6: CD68 stain highlights scattered macrophages as part of the infiltrate. (400x, CD68 immunohistochemical staining)

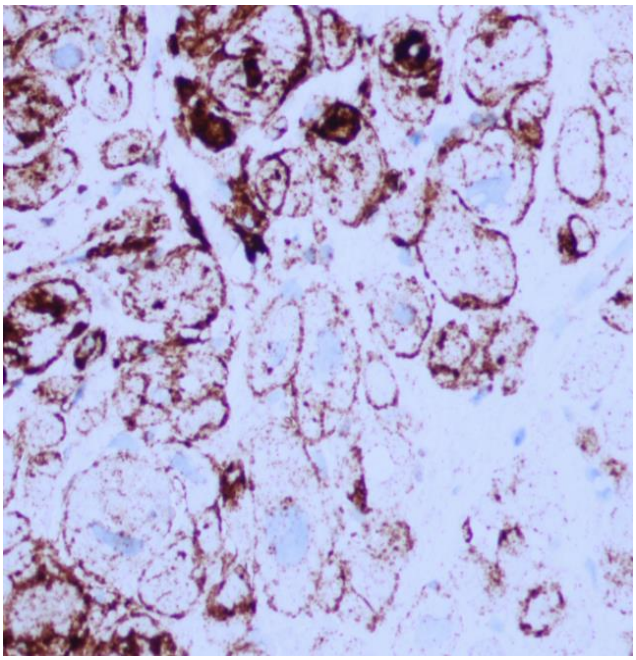

Figure 7: Myofibers show expression of PD-L1. (400x, PD-L1 immunohistochemical staining)

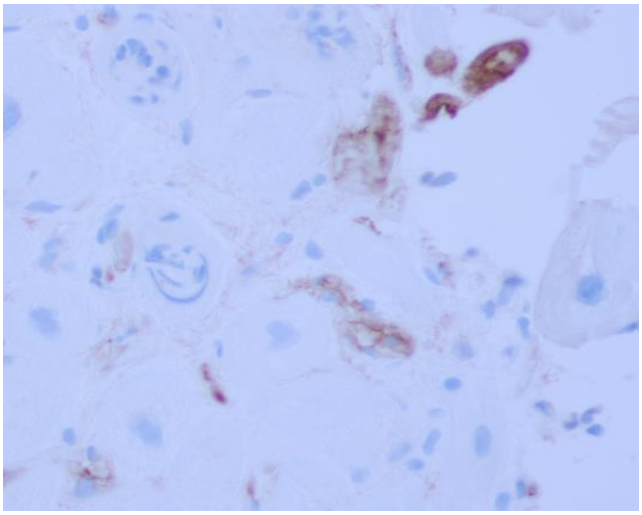

Figure 7: C4d immunohistochemical staining highlights damaged myofibers. (400x, C4d immunohistochemical staining)

Diagnosis:

Immune checkpoint inhibitor myocarditis

Differential diagnoses:

1. Viral myocarditis (e.g. Coxsackie B virus, parvovirus B19 etc.)
2. Other Drug-Induced cardiotoxicities
3. Stress (Takotsubo) cardiomyopathy

Discussion:

Checkpoint inhibitor myocarditis is an unfortunate pathology, with a high mortality, that results from the usage of immune checkpoint inhibitor (ICI) drugs to treat various cancers. ICI-drugs generally work on two mechanisms of action:

1. CTLA-4 is an antigen that blocks excessive proliferation of T-cells. T-cells, however, are necessary to eradicate tumors. Therefore, drugs like *ipilimumab* target CTLA-4, which in-turn, up-regulates T-cells to fight off cancers.
2. PD-1 and PDL-1 (programmed cell death) target T-cells for apoptosis. Therefore, drugs like *nivolumab* and *avelumab* target the destruction of PD-1 and PDL-1, which in-turn up-regulate T-cells.

The T-cell proliferation necessary to eradicate cancerous tumors, is also the pathogenesis of myocarditis. Many studies suggest that the same antigen on tumors for T-cell targeting are also found on the heart muscle. Other theories propose that PD-L1 expression for the heart itself is protective. Therefore, increasing the arrival of T-cells to the heart, while also removing protective mechanisms with PD-L1, leads to a chaotic environment of inflammation in the heart.

Immunohistochemistry: Histology showcased staining for PD-1 marker, which is consistent with the above mechanisms. C4d marker was also positive, indicative of complement activation. CD68 was positive, indicating the presence of macrophages (lymphohistiocytic infiltrate). Lastly, CD3, a marker for T-cells, was positive, confirmatory of myocarditis.

H&E staining: H&E staining was notable for inflammatory infiltrate and myocardial necrosis, both of which are required for diagnosis of myocarditis (*Dallas Criteria*).

Based on a host of markers for inflammation and histologic features of myocarditis (per Dallas criteria), a diagnosis of immune checkpoint inhibitor myocarditis is confirmed which was prompted from the usage of Nivolumab for melanoma.

References:

1. Wang C, Zhao G, Zhang Z, Yang L, Liu S, Li G, Wang H, Huang J, Wang S, Li N. Immune checkpoint inhibitor-associated myocarditis: a systematic analysis of case reports. Front Immunol. 2023 Oct 9;14:1275254. doi: 10.3389/fimmu.2023.1275254. PMID: 37876928; PMCID: PMC10590906.
2. Palaskas N, Lopez-Mattei J, Durand JB, Iliescu C, Deswal A. Immune Checkpoint Inhibitor Myocarditis: Pathophysiological Characteristics, Diagnosis, and Treatment. J Am Heart Assoc. 2020 Jan 21;9(2):e013757. doi:

10.1161/JAHA.119.013757. Epub 2020 Jan 21. PMID: 31960755; PMCID: PMC7033840.

3. Sobol I, Chen CL, Mahmood SS, Borczuk AC. Histopathologic Characterization of Myocarditis Associated With Immune Checkpoint Inhibitor Therapy. Arch Pathol Lab Med. 2020 Nov 1;144(11):1392-1396. doi: 10.5858/arpa.2019-0447-OA. PMID: 32150459; PMCID: PMC8445131.
1. Champion, S.N., Stone, J.R. Immune checkpoint inhibitor associated myocarditis occurs in both high-grade and low-grade forms. *Mod Pathol* 33, 99–108 (2020). https://doi.org/10.1038/s41379-019-0363-0