CASE REPORT

PATHOLOGY/BIOLOGY

Fatal Myocarditis Following Treatment with the PD-1 Inhibitor Nivolumab

ABSTRACT: Therapeutic antibodies targeting the programmed cell death protein 1 (PD-1) pathway function as immune checkpoint inhibitors, allowing the immune system to recognize tumors which otherwise escape immune surveillance. However, these agents can also elicit an autoimmune response by inhibiting the ability of non-neoplastic tissues and regulatory cells to suppress the immune system. Here we present a fatal case of active myocarditis in a 55-year-old man with non-small-cell lung cancer which occurred following monotherapy with the PD-1 inhibitor nivolumab (Opdivo). He presented with acute right-sided heart failure and died 1 day after admission. Postmortem examination revealed multiple gelatinous lesions in the myocardium of the interventricular septum and the bilateral atria and ventricles which had microscopic features diagnostic of myocarditis. Subsequent studies failed to identify an infectious cause. Immune checkpoint inhibitors are an increasingly common addition to anticancer regimens and they should be considered in the evaluation of acute myocarditis.

KEYWORDS: forensic science, myocarditis/pathology, myocarditis/immunology, programmed cell death 1 receptor, drug effects, nivolumab, immunotherapy/adverse effects, autopsy

Immune checkpoint inhibitors are a rapidly expanding family of therapeutics that are increasingly utilized in the treatment of cancer (1). Nivolumab is an IgG4 monoclonal antibody that binds programmed cell death protein 1 (PD-1) on the surface of lymphocytes (2). This allows the immune system to recognize and destroy tumor cells which otherwise evade the immune response. While side effects are typically mild, serious adverse reactions related to autoimmunity can occur (3). Recently, cases of acute myocarditis have been reported in patients on mono- and combination therapy with immune checkpoint inhibitors (4–7). Here, we report a case of fatal myocarditis following treatment with nivolumab and we detail our findings at autopsy. As immune checkpoint inhibitors come into widespread use, it will be important to consider them in the differential diagnosis of acute myocarditis.

Case Report

A 55-year-old man with diagnoses of pulmonary adenocarcinoma, hypertension, and COPD received his first dose of the PD-1 inhibitor nivolumab (Opdivo, 3 mg/kg) 49 days prior to death. He reported no adverse effects and received a second dose 21 days later. Within 3 days of receiving the second dose, he presented to the emergency department in diabetic ketoacidosis (blood glucose = 1409 mg/dL) and received a diagnosis of new-onset insulin-dependent diabetes mellitus likely secondary to nivolumab treatment. He was stabilized and ultimately discharged home on insulin.

He had an unremarkable course for the next 19 days until 2–3 days prior to death when he reported lethargy and shortness of breath despite normal blood glucose readings. EMS was called and he was found alert and oriented in a wide complex ventricular tachycardia with cool limbs. He was transported to our hospital where he underwent successful cardioversion. Additional testing revealed an elevated troponin I (14.43 ng/mL, normal 0.0–0.3 ng/mL). CT angiogram was negative for pulmonary embolus. A transthoracic echocardiogram demonstrated a dilated right ventricle and atrium with reflux into the hepatic veins, suggestive of right heart failure. Cardiac catheterization revealed greatly elevated right-sided filling pressures and no acute coronary artery lesions. He also had acute kidney injury likely secondary to cardiogenic shock and received one cycle of hemodialysis. He was diagnosed with acute decompensated right-sided heart failure with cardiogenic shock and multi-organ failure. Despite maximal medical intervention, he was pronounced dead 1 day after admission and the family consented to an autopsy.

At autopsy, external examination was notable only for evidence of recent medical intervention. Internal examination revealed cardiomegaly (680 g) and multiple gelatinous lesions in the interventricular septum and bilateral atria and ventricles measuring up to 1.5 cm in greatest dimension (Fig. 1). Histologic sections of myocardium showed diffuse lymphoplasmacytic infiltrates with
foci of active myocyte injury and necrosis throughout the atria, ventricles, and interventricular septum (Fig. 2A–B). Sections of the larger lesions revealed early granulation tissue formation with many hemosiderin-laden macrophages (Fig. 2C). Significant numbers of eosinophils or neutrophils were not identified.

IHC for CD3 (Ventana), CD4 (Ventana), CD8 (Ventana), and CD20 (Cell Marque) showed a mixed population of CD3-positive T cells with a CD4:CD8 ratio of 1:2 and scattered CD20-positive B cells (Fig. 3A–D). Because nivolumab is an IgG4 antibody that targets membranous PD-1 protein on lymphocytes, we also performed IHC for IgG4 (Cell Marque) to determine whether we could identify lymphocytes with membranous IgG4 staining that might indicate occupancy by nivolumab. However, IgG4-positive lymphocytes were not identified.

The gross, histologic, and IHC findings were consistent with either a viral or autoimmune mediated myocarditis, and we sought to differentiate between these two possible etiologies. All blocks of myocardium were sent to the Center for Disease Control and Prevention (CDC)—Infectious Diseases Pathology Branch to assay for the presence of viral DNA. Testing identified parvovirus B19 genomic DNA. However, parvovirus B19 has a prolonged latency period in tissues and its DNA is frequently detected in heart tissues from autopsies of patients with no clinical or histopathologic evidence of myocarditis (8,9). To determine whether active parvovirus B19 virus was present, we performed IHC for viral capsid protein on sections of myocardium using an anti-parvovirus B19 VP1/VP2 antibody (Millipore, clone R92F6) (10). This revealed no evidence of viral particles.

Finally, we sought to determine whether the T-cell infiltrate within the myocardium was related to the tumor-reactive T cells that were produced following nivolumab therapy. We extracted genomic DNA from sections of the decedent’s myocardium and lung tumor and amplified T-cell receptor genes (gamma and beta) by PCR. We then measured and compared the fragment sizes of these products and determined the presence or absence of clonality using established guidelines (11,12). This demonstrated multiple dominant, clonal populations of T cells, which were shared across both samples.

Additional findings at autopsy included heavy lungs bilaterally (left: 1670 g, right: 950 g) with a mass-like area of consolidation in the right upper lobe (16 × 5.5 × 4.2 cm), and focally severe atherosclerotic heart disease with maximal stenosis of 90% in the proximal first diagonal branch of the left anterior descending artery. Histologic sections of lung tissue revealed residual tumor cells associated with extensive fibrosis and therapy-related changes. Sections of pancreas revealed extensive changes of atrophy, scant lymphoplasmacytic infiltrates, and no identifiable islet cells.
The cause of death in this case was acute myocarditis, based on the prominent gross and histologic findings in the heart, and the patient’s well-documented terminal history. The myocarditis was likely secondary to nivolumab treatment. In support of this, the T cells present in the myocardium were clonally identical to the tumor-reactive T cells in the lung tumor, and the patient had clinical evidence of autoimmune disease with new-onset diabetes mellitus. The suspected mechanism of death is arrhythmia due to ongoing myocarditis and granulation tissue formation in the interventricular septum. The manner was ruled natural.

Discussion

Myocarditis is an inflammatory disease of heart muscle which can be the result of acute infections, postinfectious immune-mediated syndromes, exogenous agents, and idiopathic etiologies which are apparently noninfectious but immune-mediated (13–15). The yearly incidence of myocarditis is estimated at 1–10 cases per 100,000 persons and is similar across race and sex. The median age of diagnosis is 42, although it occurs across all age groups. Young males appear to be particularly susceptible, as well as immunocompromised persons, pregnant women, and neonates. The clinical presentation of myocarditis is highly variable. Many patients have no symptoms, while others may develop acute heart failure, postmyocarditis cardiomyopathies, or present with sudden death. Histologic examination of myocardial tissue showing lymphocytic infiltrates associated with myocardial necrosis is the gold standard for diagnosis.

Nivolumab is a PD-1 inhibitor that was originally approved by the FDA for the treatment of metastatic melanoma in 2014 and has since received approval for the treatment of non-small-cell lung cancer (NSCLC), renal cell carcinoma, urothelial carcinoma, squamous cell carcinoma of the head and neck, and classical Hodgkin lymphoma (2). It is a member of an expanding class of immune checkpoint inhibitors, including pembrolizumab (Keytruda), atezolizumab (Tecentriq), avelumab (Bavencio), durvalumab (Imfinzi), and ipilimumab (Yervoy). While typically well tolerated, these agents may cause severe life-threatening reactions involving the lungs, gastrointestinal tract, endocrine glands, liver, and brain (3,16,17). Adverse reactions are more common when used in combination with other immune checkpoint inhibitors. However, myocarditis has not traditionally been associated with these agents and was not significantly linked to nivolumab monotherapy during initial clinical trials (2,18).

Recently, there have been reports of acute myocarditis following treatment with nivolumab alone and in combination with other immune checkpoint inhibitors (4–6,19–21). In one detailed report of two patients who received combination nivolumab and ipilimumab therapy, the patients died after developing rhabdomyolysis followed by early and refractory electrical instability (6). At autopsy, the myocardium was infiltrated by a T-cell and macrophage-rich infiltrate, and T-cell clonality studies showed that the T-cell populations in the myocardium were clonally identical to T cells found in the tumors of the decedents. The decedent in our case similarly had a T-cell-rich myocardial infiltrate, developed electrical instability, and likely died of a lethal cardiac arrhythmia. We also identified shared T-cell clones in the decedent’s myocardium and tumor.

In our case, the CDC identified parvovirus B19 genomic DNA in the myocardium. Parvovirus B19 is commonly associated with erythema infectiosum (fifth disease) and aplastic anemia (22). Following infection, the viral genome may exist in a latent state within the peripheral tissues for prolonged periods. For this reason, parvovirus B19 DNA can be routinely identified in hearts of
both living patients and decedents at rates ranging from 12 to 69%, depending on the detection method (8,9). In contrast, parvovirus B19 myocarditis is exceptionally rare (23,24). When it causes myocarditis, it is reported to form foci around capillaries and contribute primarily to diastolic dysfunction without causing significant myocyte necrosis. In contrast, our case featured extensive regions of myocyte necrosis and pan-myocardial inflammation, which did not form foci around capillaries. Moreover, the decedent presented with right-sided systolic heart failure. Finally, we performed IHC for parvovirus B19 viral particles, which was negative. Thus, it is unlikely that the acute and fatal myocarditis in this case was due to parvovirus B19.

There are now six FDA-approved immune checkpoint inhibitors on the market which continue to receive expanded approval to target additional cancer types (25). As a result, the number of patients receiving these agents is rapidly increasing. In the forensic setting, it is now critical to consider immune checkpoint inhibitors when decedents present with a history and pathology consistent with myocarditis. We believe that once infectious etiologies have been ruled out, identifying shared T-cell clonality consistent with myocarditis is reported to form foci around capillaries. Moreover, the decedent presented with right-sided systolic heart failure. Finally, we performed IHC for parvovirus B19 viral particles, which was negative. Thus, it is unlikely that the acute and fatal myocarditis in this case was due to parvovirus B19.

There are now six FDA-approved immune checkpoint inhibitors on the market which continue to receive expanded approval to target additional cancer types (25). As a result, the number of patients receiving these agents is rapidly increasing. In the forensic setting, it is now critical to consider immune checkpoint inhibitors when decedents present with a history and pathology consistent with myocarditis. We believe that once infectious etiologies have been ruled out, identifying shared T-cell clonality consistent with myocarditis is reported to form foci around capillaries. Moreover, the decedent presented with right-sided systolic heart failure. Finally, we performed IHC for parvovirus B19 viral particles, which was negative. Thus, it is unlikely that the acute and fatal myocarditis in this case was due to parvovirus B19.

Acknowledgments

We would like to acknowledge the University of Wisconsin Carbone Cancer Center—Experimental Pathology Laboratory for assistance with performing IHC for parvovirus B19.

References


Additional information and reprint request:
Daniel R. Matson, M.D., Ph.D.
Department of Pathology and Laboratory Medicine,
University of Wisconsin School of Medicine and Public Health
UWCH - Rm A4/204 - 3224
600 Highland Avenue
Madison, WI 53792, USA
E-mail: DMatson@uwhealth.org