

Case Report

A Case of Full Recovery from Prolonged Cardiac Arrest after Infusion with Paclitaxel and Pembrolizumab

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Keywords

Cardiotoxicity · Immunotherapy · Chemotherapy · Lung cancer

Abstract

Lung cancer is one of the most common cancers and has the highest risk of mortality in both genders. This devastating cancer is also a significant financial and emotional burden to patients and the healthcare system. Chemotherapy and immunotherapy have become the cornerstone for the treatment of lung cancer. However, treatment may come with severe and sometimes fatal side effects. In this report, we present the case of a 52-year-old Caucasian male who suffered two episodes of prolonged cardiac arrest after the infusion of paclitaxel and pembrolizumab.

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Introduction

Lung carcinoma is the 2nd most common cancer diagnosis by gender, behind prostate cancer for men and breast cancer for women [1]. Lung cancer has a very guarded prognosis. Chemotherapy has been used to treat lung cancer for many years. Immunotherapy, particularly therapies targeting the PD-1/PDL-1 pathway, has emerged as a promising new treatment option for several cancers including lung cancers [2]. A double-blind phase 3 trial evaluated the combination of pembrolizumab and platinum-based chemotherapy in patients with metastatic nonsmall cell lung cancer and found that the 12-month overall survival (OS) was 69.2%, and progression-free survival (PFS) was 8.8 months in the pembrolizumab-

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combination group, whereas 12-month OS was 49.4%, and PFS was 4.9 months in the placebo-combination group [3]. In both groups, the most common adverse events were nausea, anemia, and fatigue. Adverse events leading to death occurred in 27 of 405 patients (6.7%) in the pembrolizumab-combination group and in 12 of 202 patients (5.9%) in the placebo-combination group [3]. Thus, both chemotherapy and immunotherapy can lead to serious toxicities. One of these serious toxicities which can be life-threatening as well is cardiotoxicity. Jakubowski and Kemeny showed that cardiotoxicity occurs in 6% of the patients receiving cisplatin and 5-fluorouracil (5-FU) [4]. One of the studies evaluated 538 patient records who were treated with anti-PD-1/anti-PDL1-based immunotherapy and found that 34 cardiac events occurred. The most common were pericarditis (2.2%), atrial fibrillation (AF) with rapid ventricular response (2%), and heart failure (1.5%) [5]. In the case that we have described, the 52-year-old Caucasian male developed two episodes of prolonged cardiac arrest while undergoing paclitaxel (PTX) and pembrolizumab therapy. Thankfully, the patient recovered from both these episodes.

Case Presentation

We present the case of a 52-year-old male with 18 pack-year smoking history and past medical history of stage IV nonsmall cell lung cancer, bicuspid aortic valve, and hypertension, who had two episodes of cardiac arrest related to PTX and pembrolizumab infusion. The patient initially presented to the hospital in September 2018 for 1 month of fatigue, night sweating, and weight loss. At baseline, the patient received extensive workup, including CT of the chest, abdomen, pelvis, MRI of the brain, complete blood count with differentials, comprehensive metabolic panel, electrocardiogram (ECG), and transthoracic (TTE) echocardiogram (ECHO). A 2.4 cm lesion was noticed in his left lower lobe lung, with an endobronchial component and associated partial atelectasis (Fig. 1). Mediastinal, bilateral hilar, right supraclavicular lymphadenopathy, and a suspicious 1.8-cm lytic lesion in the distal right clavicle were also observed (Fig. 2). There was no evidence of other distant metastatic diseases. A bone biopsy was performed, and the patient was confirmed to have stage IV lung squamous cell carcinoma (Fig. 3, 4). Patient's PD-L1 was 1–49%. Laboratories were unremarkable, ECHO was normal with ejection fraction of 71% (normal 50–75%) and ECG showed no abnormalities (Fig. 5). There was no history of cardiac ischemia or heart disease in either the patient or his family. The decision was made to start the patient on a combination of immunotherapy and chemotherapy. Patient was seen and examined by the treating physician prior to the start of the treatment and did not have any significant health issues except for mild fever and night sweats. The patient was first premedicated with dexamethasone, diphenhydramine, famotidine, and ondansetron followed by carboplatin, PTX, and pembrolizumab, and he tolerated the treatment well. Twenty-one days later, the patient came back to the hospital for cycle two treatment. The patient was examined by the treating physician prior to the treatment and had no new health complaints and mentioned that the mild fever and night sweats which were present on day one treatment have improved. The patient received the same premedication regimen mentioned above after which the patient started pembrolizumab infusion of 30 min, which was completed without any incident. The patient then started PTX infusion and within 8–10 min of the infusion initiation, the patient started complaining of nausea, tingling of feet, followed by an episode of vomiting and urination. Very shortly, A code blue was called. The patient was found unresponsive with pulseless electrical activity (PEA) cardiac arrest. Cardiopulmonary resuscitation (CPR) and advanced cardiac life support were initiated immediately. One dose of 1 mg epinephrine was given subcutaneously due to loss of peripheral intravenous access, and 3 rounds of CPR were provided before EMS

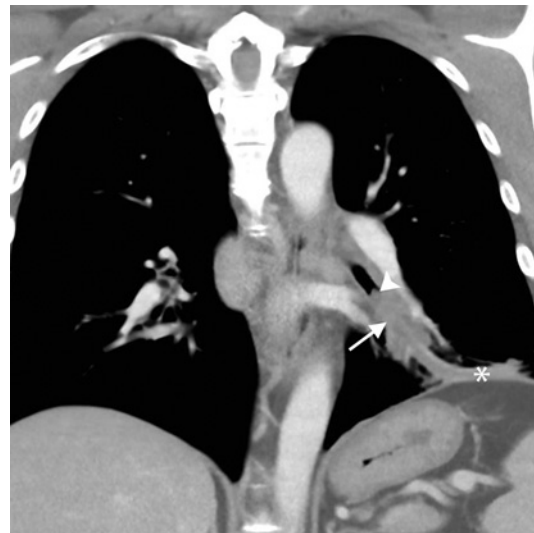


Fig. 1. Lung mass.

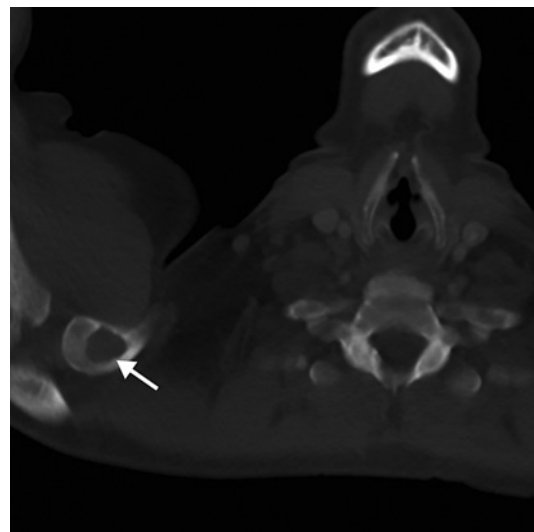


Fig. 2. Bone metastasis.

arrived. Pulse and rhythm were checked, but the patient was found PEA simultaneously, and therefore, no shock was delivered. After airway management and IV access were placed, the patient was transferred to Emergency Department (ED). During the transportation to the ED, the patient was found to have ventricular fibrillation and received 2 shocks on the route to the ED. On Admission to the intensive care unit (ICU), the patient received bilateral chest tubes, had central internal jugular line and right femoral arterial line placed, and was also intubated. The patient received propofol and epinephrine drip, rewarmed due to hypothermia, and was consulted by cardiologist and neurologist due to suspected anoxic encephalopathy. ECG, TTE, cardiac catheterization, computed tomography of head without contrast and troponins were ordered together with comprehensive metabolic panel, complete blood count with differentials, and arterial blood gas. The patient regained a pulse and cardiac activity after 45 min of resuscitation. Shortly thereafter while in the ICU, patient had another episode of PEA cardiac arrest which lasted 8 min before the return of spontaneous circulation the second time after CPR.

On the TTE, it was noted that the patient had biventricular heart failure with TTE showing left ventricular ejection fraction (LVEF) of 33% and abnormal systolic function with regional

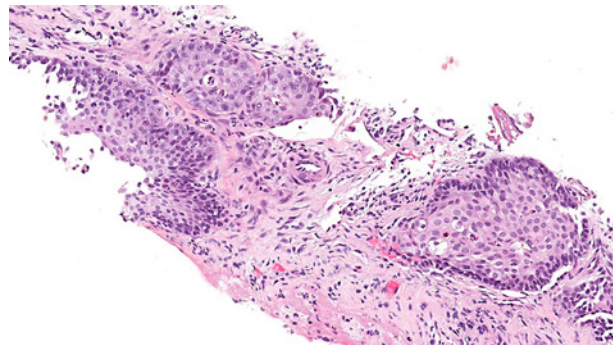


Fig. 3. Keratinization in squamous cell carcinoma.

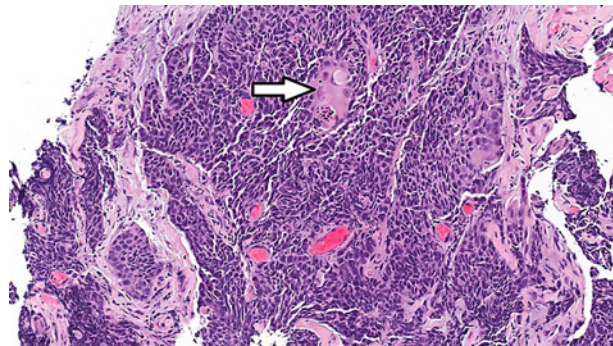


Fig. 4. Squamous cell atypia in squamous cell carcinoma.

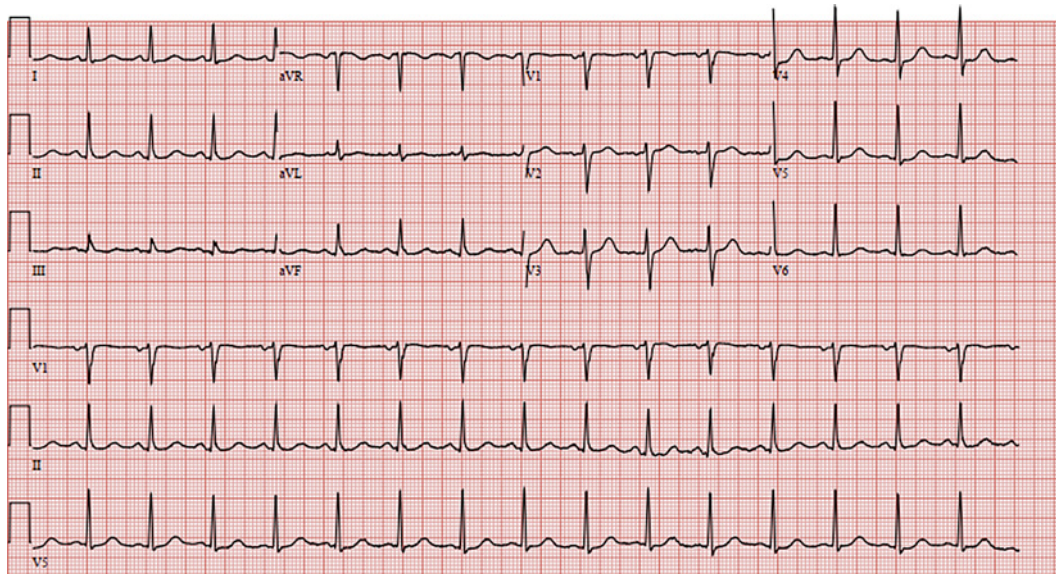


Fig. 5. Baseline ECG.

wall abnormalities. The patient's baseline LVEF done 2 months prior was 71%, with normal ventricular function. The ECG showed a new-onset right bundle branch block (Fig. 6) compared to the baseline ECG which was normal. Laboratories and CT head without contrast were normal. A timeline of ECG findings and EF from baseline to follow up is included in Table 1. The patient

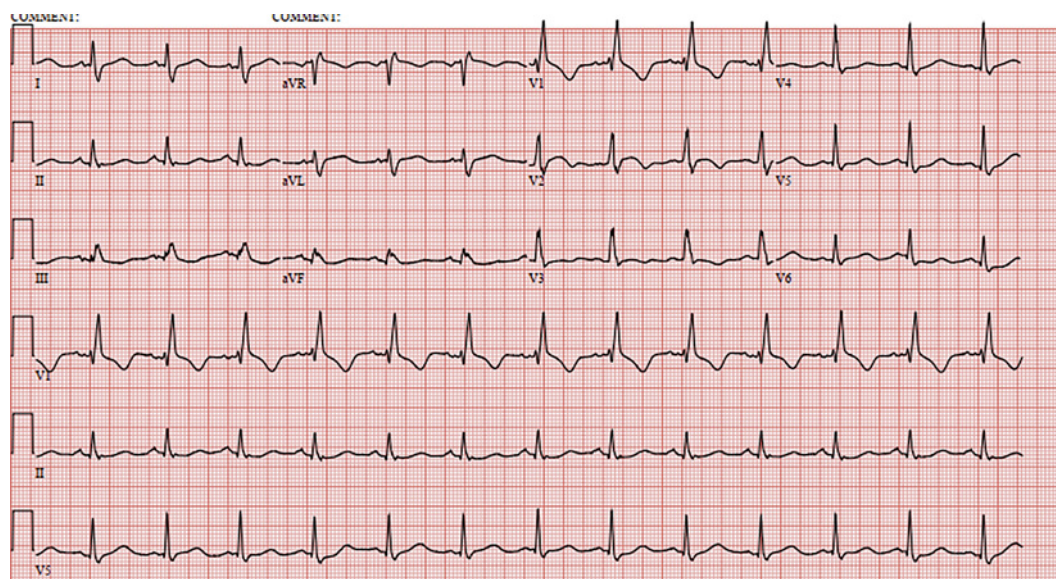


Fig. 6. ECG post-cardiac arrest which showed RBBB.

Table 1. Timeline of ECG and EF changes in the patient from baseline to follow up after the event

Test	Baseline	Admission	Discharge	Follow-up
ECG	Normal ECG	RBBB with RVH	RBBB resolved, T-wave abnormalities	Normal ECG
EF [normal 50–75%], %	71	33	63	67

also had cardiac catheterization during the ICU stay, and no abnormal findings were noticed. Before discharge, a repeat ECG and ECHO were done 5 days after admission. The TTE showed a normal left ventricular chamber size with normal systolic function, LVEF of 63%, and no regional wall motion abnormalities, while the previously noted right bundle branch block was no longer visible on the ECG. The patient's functional status and neurologic function continued to improve, and he was successfully discharged home 9 days after admission. The patient has fully recovered and received other anticancer treatments after this incident, including carboplatin, gemcitabine regimen followed by durvalumab and tremelimumab through a clinical trial. No further cardiac incidents occurred. A follow-up TTE and ECG were done 4 months later and showed no abnormalities.

Discussion

Lung cancer is one of the most causes of mortality in the USA and worldwide [1, 6, 7]. It leads to substantial financial burden at individual and public levels [6]. For the past several decades, multiple regimens of treatments have been introduced to treat metastatic lung cancer to prolong the OS of patients while maintaining a desirable quality of life. The approval of immunotherapy agents targeting the PD-L1/PD-1 pathways has become a revolutionary advancement in managing many cancer types, including lung cancer [2]. However, only a subset of patients has benefited from these treatments alone, and thus, most lung cancer patients will require a combination of chemotherapy and immunotherapy.

The combination of immunotherapy and chemotherapy has significantly improved outcomes in various cancers. In triple-negative breast cancer, the IMpassion130 and KEYNOTE-355 trials both demonstrated a substantial PFS benefit with the addition of anti-PDL1 therapy to chemotherapy [8, 9]. Serious adverse events occurred in 103 patients (22.8%) in the anti-PDL1 plus chemotherapy group and in 80 (18.3%) patients in the chemotherapy group in IMpassion 130 trial [8]. At the updated descriptive analysis of IMBrave150, the median OS of 19.2 months with atezolizumab plus bevacizumab versus 13.4 months with sorafenib showed a median 5.8-month increase in survival with the combination in patients with advanced HCC [10]. The extended follow-up results of the phase 3 KEYNOTE-426 trial of patients with previously untreated advanced renal cell carcinoma showed that treatment with pembrolizumab plus axitinib resulted in a reduced risk of disease progression or death versus treatment with sunitinib [11]. Serious adverse events like acute coronary syndrome, acute myocardial infarction, cardiac failure, cardiac tamponade, myocarditis occurred in 1 patient each and cardiac arrest in 2 patients in pembrolizumab plus axitinib group [11]. Thus, combining immunotherapy with various chemotherapies is associated with higher efficacy. However, it may be accompanied by serious, and sometimes fatal, side effects like cardiotoxicity. Cardiotoxicity, one of the most concerning side effects, can be caused by some types of chemotherapeutic agents used to treat neoplastic diseases and has an undesirable impact on prognosis and quality of life [12]. The incidence of cardiotoxicity differs depending on multiple factors, including the type of drug, cumulative dose, schedule of dose administration, route and combination with other cardiotoxic drugs, patient age, and cardiovascular history [13]. The onset of these effects is not unique and can happen anytime, including early during therapy or a year later after completing therapy [12]. Acute cardiotoxicity can develop from the initiation of treatment to until 2–4 weeks after therapy and is characterized by reversible arrhythmias, abnormalities in ventricular repolarization, prolongation of QT interval, and acute coronary syndrome [14]. Chronic cardiotoxicity is divided into early and late cardiotoxicity, which appears either within the first year after treatment or more than 1 year after chemotherapy. Chronic cardiotoxicity includes reversible or irreversible cardiac dysfunction (systolic or diastolic), leading to irreversible heart failure and even death [15, 16]. The mechanisms by which cardiotoxic chemotherapeutic agents affect cardiac cells are not well known. The cardiomyocyte effects of chemotherapy are divided into two. (A) An irreversible oxidative stress leading to the death of cardiomyocytes; (B) reversible cardiomyocyte damage [12]. Systolic dysfunction leading to heart failure is the common cause of what can be described as chemotherapy-induced cardiomyopathy [14]. However, other complications like hypertension and arrhythmias, as in our patient, have been documented [13, 17, 18]. PTX is an antimicrotubular agent used to treat several solid tumors [19]. However, its use may result in cardiovascular toxicities [19, 20], including arrhythmias, myocardial infarction [21, 22], and AF. PTX, discovered in 1962, is a mitotic spindle inhibitor [23]. Coronary artery vasospasm by PTX has been mentioned in the literature [21]. Other researchers reported that PTX-induced cardiotoxicity occurs either indirectly following a massive histamine release with subsequent conduction disturbances and arrhythmia or through direct myocardial damage occurring on subcellular organelles, which may result in congestive heart failure [23, 24].

The patient in our case report experienced PEA and heart failure. A TTE done after the cardiac event showed dilated cardiomyopathy with an ejection fraction of 33%, leading to systolic biventricular heart failure with two episodes of cardiac arrest lasting 45 and 8 min, respectively. Of note, this subject's ECHO before and after the cardiac arrest was 71% and 63%, respectively, confirming the transient nature of heart failure. This is also supported by the follow-up ECG and ECHO done 4 months after the cardiac arrest incident. In addition to drug toxicities, PTX is known to induce hypersensitivity reaction (HSR), an event mediated through immunological response with symptoms ranging from mild pruritus to anaphylaxis.

HSR to PTX is primarily due to type I reactions to cremophor (polysorbate 80), the pharmaceutical vehicle of PTX [25]. Allergen-specific CD4+ T-cells are known to play a crucial role in type I allergy, and the role of PD-1 signaling in limiting CD4+ T cell responses toward aeroallergens has been previously demonstrated [26]. This raises the question whether the cardiac arrest observed in the patient could represent a PTX related HSR that was augmented by PD-1 blockade.

Immune checkpoint inhibitors (ICIs) have become an essential part of cancer treatment regimens for a variety of tumors, including lung cancer. Although their introduction has revolutionized cancer management, their role in cardiotoxicity cannot be ignored. While mechanisms by which the ICIs cause cardiotoxicity have not been fully studied, cases of severe ICI-induced cardiovascular toxicities have been reported. Six cases of cardiovascular events, two of which resulted in death after Ipilimumab, have been reported [27]. Cardiac arrests after pembrolizumab administration on separate occasions were also reported [27]. The risk of cardiac toxicity depends on cumulative dose, drug administration rate, age, female gender, pre-existing heart disease, and hypertension [28]. Cardiotoxicity is one of the immune-related adverse events encountered after treatment with ICIs like pembrolizumab, and though rare, it can be fatal [29]. Cardiotoxicity by ICIs can have inflammatory or noninflammatory character leading to cardiac events, including myocarditis and left ventricular dysfunction; coronary vasospasm, Takotsubo-like symptoms, and arrhythmias, respectively, with myocarditis being the most common immune-related adverse events – induced cardiotoxicity followed by pericardial and conduction abnormalities [29].

While our understanding of mechanisms leading to cardiotoxicity in both Taxol-based chemotherapy and ICIs is evolving, there are inflammatory processes in both categories [23, 24, 29], but there are several differences. For Taxol-induced cardiotoxicity, histamine release and vasospasm mechanisms have been reported [21, 23, 24], while in ICI-induced cardiotoxicity the main mechanism is the infiltration of CD4 and CD8 T lymphocytes which is especially true for ICIs-induced myocarditis which is the leading manifestation of cardiotoxicity [29]. The other mechanism is the expansion of T-cells which target a shared antigen between the tumor and the heart [30]. Conduction abnormalities, including AF, atrioventricular block, and ventricular arrhythmias are commonly seen in ICI-associated cardiotoxicity [31]. PD-1 is known to protect against tissue inflammation and myocyte damage. Mice with PD-1 deficiency developed spontaneous myocarditis. There are no predictive biomarkers that can help identify which patients might be at risk for Immune-related cardiotoxicity [32]. The prognosis of ICI-induced myocarditis is extremely poor. The mortality rate is around 50% [32, 33]. The outcome and symptomatology in both Taxol and ICI-induced cardiotoxicity seem to be similar, including cardiac ischemia and arrhythmias with subsequent heart failure [21, 22, 29], and high rates of fatality, particularly in immune-related cardiotoxicity [29].

While cardiac arrest cases have been reported in patients treated with Taxol or ICIs, it is difficult to pinpoint a particular causative agent in our patient, as he was receiving both drugs at the same time. While we cannot conclude with high certainty, we suspect that this combination may have a synergetic effect and led to the cardiac arrest, knowing that the patient continued to receive another line of therapy, including durvalumab and tremelimumab, after this incident. However, the role of this combination therapy in cardiac arrest needs to be investigated with further research. Currently, there are no clear guidelines explicitly devised for the treatment of chemotherapy-induced toxicity. In addition to reducing the cumulative dose, administering infusions slowly compared to boluses or liposomal encapsulations might reduce the risk. Tissue velocity imaging which can assess myocardial systolic velocities, and speckle tracking, which can measure LV deformation, may help predict subclinical cardiac dysfunction, and predict impaired LV function. The presence of diabetes

mellitus, hypertension, mediastinal radiation, elderly age, and PTX treatment in the metastatic or recurrent setting predicts poor prognosis [34]. Elevation of cardiac biomarkers, including troponin and creatinine kinase MB, is almost always present in myocarditis associated with ICI therapy. The degree of elevation may correlate with major cardiac events. Glucocorticoid therapy improves left ventricular function in patients with ICI-mediated cardiotoxicity. Other targeted immune modulators may be utilized depending on the clinical course of individual patients. In addition to immunosuppression, patients should be treated with standard cardiac therapy. There is an urgent need to develop guidelines for early diagnosis and management of ICI-induced cardiotoxicity [30].

The patient in this report had a history of bicuspid aortic valve and hypertension, which could have also been a risk factor [24]. The concomitant medications, in this case, could have also been risk factors too. Although there have been multiple cases of cardiac arrests reported after administration of different anticancer medications, including chemotherapy agents and ICIs, our case represented one unusual case with prolonged and recurrent cardiac arrest after the second cycle of pembrolizumab and PTX followed by complete recovery. While we cannot definitively relate this patient's cardiac arrest to his risk factors like bicuspid aortic valve and hypertension or a combination of taxol and pembrolizumab, both of which are reported to be associated with cardiac arrest, it is imperative to have a deep understanding of the underlying mechanisms, the role of risk factors and if the combination of taxol and pembrolizumab had a cumulative negative effect on cardiomyocytes.

Conclusion

We conclude that cardiotoxicity should be taken seriously in patients undergoing chemotherapy, especially when combined with immunotherapy, both of which have been associated with cardiac arrest. Therefore, in addition to performing an extensive medical history and physical exam, a comprehensive cardiovascular evaluation, which could include EKGs and ECHO before such treatment, should be considered to determine the patients' risk and plan of intervention in the presence of possible risk factors.

Statement of Ethics

This case report was reviewed and approved by the Mayo Clinic Institutional Review Board. The patient has unfortunately passed away, and the authors tried to contact the patient's next of kin several times for the written consent but could not contact them. The Institutional Review Board approval reference number is 16-007597, and date of approval is July 10, 2016.

Conflict of Interest Statement

Yanyan Lou: advisory board: AstraZeneca, Novocure; Janssen, Lilly Oncology, Turning Point. Consultant: AstraZeneca; Honorarium: clarion health care; research funding support: Merck, MacroGenics, Tolero Pharmaceuticals, AstraZeneca, Vaccinex, Blueprint Medicines, Harpoon Therapeutics, Sun Pharma Advanced Research, Bristol-Myers Squibb, Kyowa Pharmaceuticals, Tesaro, Bayer HealthCare. Rami Manochakian: advisory board: AstraZeneca, Guardant Health, Janssen, Novocure, Takeda; consulting: AstraZeneca. Yujie Zhao: advisory board: Lilly Oncology; Coheurus Biosciences. No conflict of interest for Omar Sh Ahmed, Himil Mahadevia, Andras Khor, Jordan LeGout, and Manisha Salinas.

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Author Contributions

Omar Sh Ahmed – conception and design, collection and assembly of data, manuscript writing, final review, and approval of manuscript. Himil Mahadevia – conception and design, manuscript writing, final review, and approval of manuscript. Rami Manochakian – conception and design, manuscript writing, final review, and approval of manuscript. Yujie Zhao – conception and design, manuscript writing, final review, and approval of manuscript. Manisha Salinas – conception and design, manuscript writing, final review, and approval of manuscript. Andras Khooor – collection and assembly of data, manuscript writing, final review, and approval of manuscript. Jordan LeGout – collection and assembly of data, manuscript writing, final review, and approval of manuscript. Yanyan Lou – Conception and design, collection and assembly of data, manuscript writing, final review, and approval of manuscript.

Data Availability Statement

The patient's information is available through the Mayo Clinic medical record. All data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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