

## CASE REPORTS

# Ipilimumab-nivolumab therapy causing STEMI in a melanoma patient: A case report

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## ABSTRACT

The combination of ipilimumab and nivolumab has shown great promise in improving survival in patients with advanced melanoma. However, these novel agents are not without side effects, with adverse events occurring in up to 55% of patients on combination therapy. We report a case of ST-elevation myocardial infarction (STEMI) with resultant new severe systolic heart failure and left ventricular thrombus in a middle-aged woman with metastatic melanoma on ipilimumab-nivolumab therapy suspicious for de novo intra-arterial thrombus formation. We hypothesize that this is likely due to an immune-related adverse event, a documented phenomenon in patients on this combination therapy. To the best of our knowledge, this is the first case in patients on ipilimumab-nivolumab therapy to develop STEMI due to intra-arterial thrombus formation.

**Key Words:** Myocardial infarction, Intra-arterial thrombus, Nivolumab, Ipilimumab

## 1. INTRODUCTION

According to the World Health Organization (WHO), 130,000 new cases of skin cancer occur every year.<sup>[1]</sup> Within this group, metastatic melanoma, with a median survival of less than one year, is particularly lethal.<sup>[2,3]</sup> Most recent advances in treatment include immune checkpoint-blocking antibodies, which allow cytotoxic T-cell mediated destruction of cancer cells.<sup>[4-6]</sup> Ipilimumab, a human IgG1 monoclonal antibody that blocks cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4), has been shown to be an effective agent against advanced melanoma.<sup>[7,8]</sup> Another antibody targeted at the programmed death 1 (PD-1) receptor, Nivolumab, has been used with similar outcomes.<sup>[4,9]</sup> The combination of both of these agents has shown great promise in improving survival in advanced melanoma.<sup>[10,11]</sup>

These novel agents are not without side effects, however. Adverse events have been reported in 22%-24% of patients on ipilimumab monotherapy,<sup>[12,13]</sup> in 5%-10% of nivolumab patients,<sup>[14]</sup> and in 55% of patients on combination therapy.<sup>[9,13]</sup> These side effects include dermatitis (most common), gastrointestinal issues (including severe colitis, esophagitis, hepatitis, and pancreatitis), endocrine abnormalities (including hyperthyroidism, hypothyroidism, hypophysitis, diabetes and adrenal insufficiency), and nephritis.<sup>[15]</sup> Furthermore, cardiac conduction abnormalities and myocarditis (including fulminant myocarditis leading to death) have been reported.<sup>[16-20]</sup>

We report a case of ST-elevation myocardial infarction (STEMI) in the setting of new intra-arterial thrombus formation, severe systolic heart failure, and left ventricular throm-

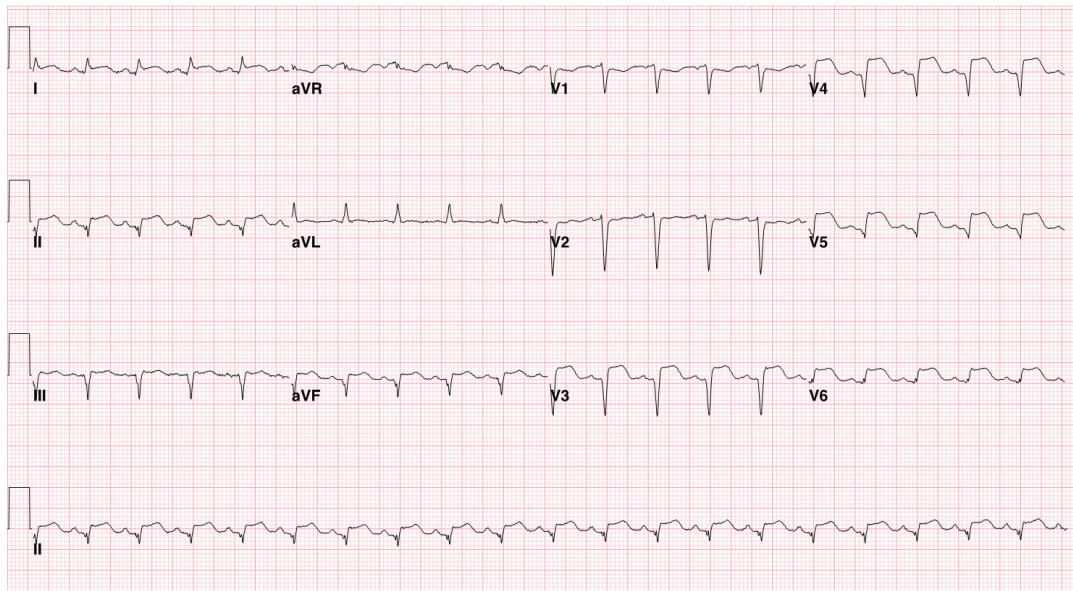
\*Correspondence: Ahmed Zaid Alkathlan, MD; Email: [ahmed.alkathlan@uhhospitals.org](mailto:ahmed.alkathlan@uhhospitals.org); Address: Department of Internal Medicine, University Hospitals Cleveland Medical Center, Cleveland, 26500 Amhearst Cir Apt 112, Beachwood, OH 44122, United States.

bus in a middle-aged woman with metastatic melanoma on ipilimumab-nivolumab therapy.

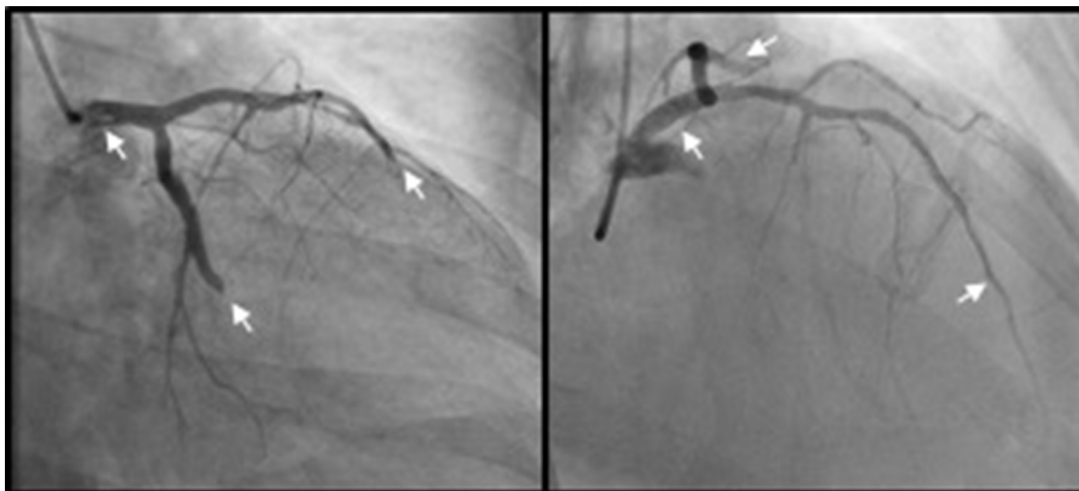
## 2. CASE PRESENTATION

The patient, a 51-year-old Caucasian female with no known coronary risk factors, was initially found to have a malignant melanoma on her back, Breslow's depth 0.5 mm (stage V)<sup>[21]</sup> in 2011. Clear margins were obtained on excision via Mohs procedure.<sup>[22]</sup> Cancer recurrence in her breast tail and axilla was diagnosed in 2016 after a core needle biopsy showed metastatic malignant melanoma with a BRAF V600E gene mutation. Positron emission tomography-computed tomography (PET-CT) detected a large hypermetabolic focus within

the left axilla, right hilar lymph nodes, subcarinal lymph node, multiple pulmonary nodules within the right lower lobe, right anterior superior iliac spine, and right iliac wing. Deemed consistent with stage IV malignant melanoma TX NX M0 based on The American Joint Committee on Cancer (AJCC) 7<sup>th</sup> edition guidelines,<sup>[23]</sup> the patient was started on Ipilimumab/Nivolumab combination therapy. Her course was complicated by pneumonitis one week after her first cycle and grade 3 colitis, which required hospitalization for IV fluids and prednisone at 1 mg/kg<sup>[24]</sup> after her third cycle. The morning after discharge, the patient developed left-sided chest tightness. On repeat admission, the electrocardiogram showed ST elevation in leads II and V3-V6 (see Figure 1).



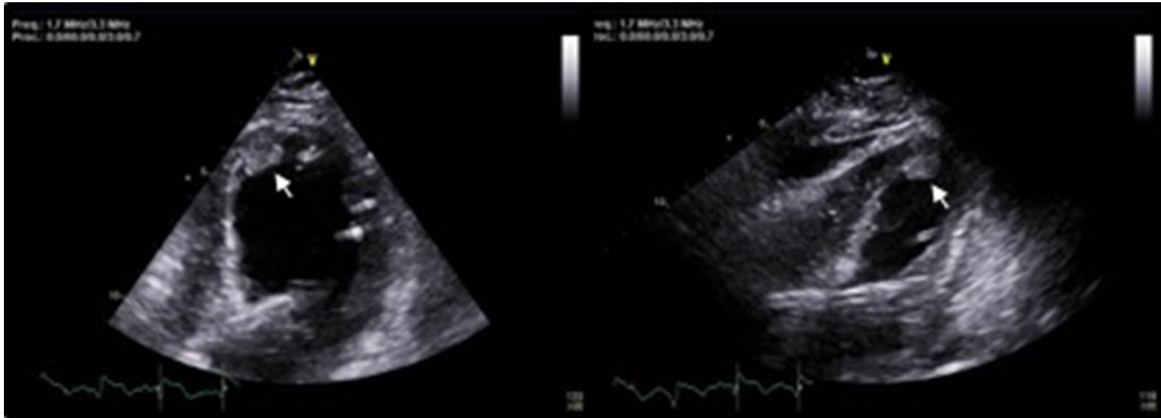
**Figure 1.** Admission electrocardiogram with ST elevations in leads II and V3-V6



**Figure 2.** Pre and post-coronary intervention angiography revealing left main coronary artery, left anterior descending coronary artery, and left circumflex coronary artery thrombus formation with good post-intervention results

With a troponin-I of 8.4 ng/ml, the patient was loaded with aspirin (324 mg) and ticagrelor (180 mg) and emergently underwent coronary angiography (see Figure 2). A heart catheterization revealed thrombi in the left main (LM) - 75% occlusion and Thrombolysis in Myocardial Infarction (TIMI<sup>[25]</sup>) flow of 2-left anterior descending (LAD)-100% occlusion and TIMI flow of 0-and left circumflex (LCX)-100% occlusion and TIMI flow of 0. The right coronary artery did not contain thrombus. Percutaneous coronary intervention

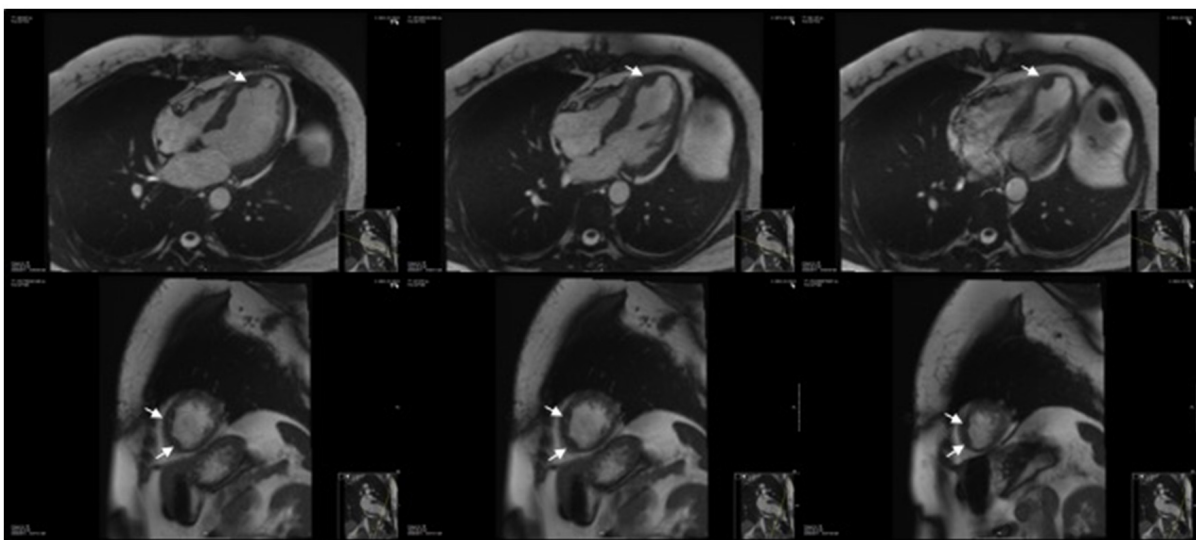
(PCI) was performed within the LM, with a successful placement of Resolute Integrity drug-eluting stent. Aspiration thrombectomy to the LAD and LCX resulted in good return flow within these vessels. Given the low cardiac index of 1.8 and elevated LVEDP, the patient underwent Impella 2.5 and Swan-Ganz catheter placement. Post-procedurally, she was started on Eptifibatide and continued on dual antiplatelet therapy.



**Figure 3.** Transthoracic echocardiography demonstrated newly reduced LVEF and LV apical mass

Transthoracic echocardiography (TTE) revealed a left ventricular (LV) estimated ejection fraction (EF) of 20%-25% and LV apical mass that was concerning for thrombus vs. metastasis (see Figure 3). Given these findings, she was restarted on intravenous heparin infusion. Troponin peaked at 162 ng/ml. Cardiac Magnetic Resonance (CMR) was pursued to better delineate the LV mass. A 14 mm × 5 mm

× 4 mm mass lesion within the LV apex adherent to the interventricular septum was noted (see Figure 4). The mass showed no enhancement with first or late pass perfusion of gadolinium, which is consistent with an LV thrombus. Extensive transmural late gadolinium enhancement consistent with nonviable myocardium involving the mid anterior, septal, and lateral myocardium as well as the entire apex was seen.



**Figure 4.** Cardiac magnetic resonance imaging verifies the presence of a new apical LV thrombus

The patient was transitioned to therapeutic enoxaparin for the LV thrombus. Given continued diarrhea, she was started on high dose intravenous methylprednisolone therapy after *C. difficile* and stool culture tests were negative. Infliximab infusion was reinitiated. She was weaned-off of mechanical support after a gradual improvement in her symptoms. She was safely discharged home on dual-antiplatelet therapy (DAPT) and prednisone with close follow-up.

### 3. DISCUSSION

As aforementioned, CTLA-4 and PD-1 inhibitors provide a new therapeutic option for an otherwise lethal disease. Given their recent approval, relatively little is known about their cardiovascular implications. Our patient was noted to have an STEMI, prompting emergent heart catheterization which showed diffuse left-sided coronary blockages. Given her lack of prior symptomatology, low-risk profile, otherwise clean coronary anatomy, and appearance of thrombi on catheterization, we hypothesize that these thrombi were induced by Ipilimumab/Nivolumab combination therapy.

Thoreau et al. have previously reported a case of intra-arterial thrombus formation in a patient on combination CTLA-4/PD-1 inhibitor therapy requiring trans-phalangeal amputation.<sup>[26]</sup> After extensive diagnostic evaluation that ruled out other possible causes, they similarly postulated that combination therapy induced thrombus formation.<sup>[26]</sup> While an animal model

has shown proinflammatory and proatherogenic effects of anti-PD-1 agents,<sup>[27]</sup> it is unlikely in either of the cases that this led to an atheromatous plaque that either embolized or ruptured given the imaging findings and time course of the clinical presentation.

We further postulate that this may be an immune-mediated event, a known phenomenon with these agents.<sup>[28]</sup> However, an exact mechanism at this time is unknown and requires further study. While most side effects are mild, 15% of such events lead to severe complications and can affect multiple organs within the body.<sup>[28]</sup> Myositis, cardiomyopathy, and conduction aberrances have all been connected to CTLA-4/PD-1 inhibitor therapy.<sup>[16-20]</sup> To our knowledge, this is the first suspected case of de novo intra-arterial thrombus formation leading to STEMI in CTLA-4/PD-1 inhibitor therapy. Given the concern for the cardiovascular effects of these agents and growing side effect profile, increased and more aggressive screening may be warranted in certain higher-risk individuals prior to initiation of therapy.

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### CONFLICTS OF INTEREST DISCLOSURE

The authors have declared no conflicts of interest.

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