

Case Report

Associated Myocarditis: A Predictive Factor for Response?

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Abstract

In the present case report, we aimed to describe 2 cases of myocarditis occurring as serious adverse effects of immune checkpoint inhibitors (ICIs) administered as treatment for metastatic melanoma. We describe 2 female patients: an 81-year-old treated with pembrolizumab and a 55-year-old treated with a combination of nivolumab and ipilimumab. Both patients underwent resection of metastases; while under treatment, both developed myocarditis, most probably as a toxicity from pembrolizumab and nivolumab plus ipilimumab, respectively. While they achieved complete response, the occurrence of myocarditis as a toxicity of ICIs may have been a predictive sign that the immune system was sufficiently activated by the checkpoint inhibitor therapy to induce complete remission.

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Introduction

Cutaneous melanoma, a malignancy whose origin is the pigment-producing cell in the skin, the melanocyte [1], accounts for 1% of all skin cancers [2]. Most melanoma cells continue to synthesize melanin, so melanoma tumors are usually brown or black. However, some melanomas do not make melanin and can appear pink, tan, or even white.

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Melanomas can develop anywhere on the skin, but they are more likely to start on the trunk (chest and back) in men and on the legs in women. The neck and face are other common sites [1]. An estimated 9,320 people die of melanoma annually in the USA, 5,990 men and 3,330 women. From 2006 to 2015, the death rate for melanoma declined by 1% per year in adults 50 years of age and older and by 2.6% per year in those younger than 50 years [3].

Metastatic melanoma can show widespread organ involvement: the lymph nodes are involved in 70–75% of cases of metastatic melanoma, areas of the skin, fat, and muscle in 65–70%, the lung in 70–87%, liver and gallbladder in 54–77%, the brain in 36–54%, bone in 23–49%, the gastrointestinal tract in 26–58%, the heart in 40–45%, the pancreas in 38–53%, the adrenal glands in 36–54%, the kidneys in 35–48%, the spleen in 30%, and the thyroid in 25–39% [4].

Over the past decade, there has been a revolution in the systemic treatment of metastatic melanoma, and patients now have more options for more effective treatment, such as targeted therapy and immunotherapy. In addition, molecular tests have been developed to select the most appropriate therapy for the individual patient.

Immune checkpoint inhibitors (ICIs) have been approved by regulatory authorities around the world for an extended range of malignancies. Along with substantially improved treatment results, including progression-free survival, overall survival, and clinical benefit, the ICIs also have led to immune-related adverse effects that in a minority of cases are life-threatening.

Myocarditis (an inflammation of the heart muscle [myocardium]) is an uncommon but potentially fatal complication of ICI therapy in which the patient may develop heart failure, QT prolongation, arrhythmias, left ventricular (LV) hypertrophy, myocardial ischemia, and infarction. However, generally, the toxicity resolves after treatment discontinuation.

The incidence of ICI-associated myocarditis is low and has been reported to range from 0.06 to 1% in patients receiving an ICI [5]. The prevalence of myocarditis as reported in a recent study was 1.14% with a median time of onset of 34 days after starting ICI (interquartile range 21–75) [6]. Myocarditis may be difficult to diagnose, so it is possible that the actual incidence is higher [5].

Case 1

A 78-year-old woman underwent excision of an ulcerated bleeding skin lesion in the left thigh area in 2015. She had noted a black lesion on her thigh since 2010. She had been treated for hypertension and hypothyroidism. She had no family history of cancer and did not smoke.

The excisional biopsy showed ulcerated nodular malignant melanoma Clark Level 4. Subsequently, on November 29, 2015, she underwent wide excision of the area of the biopsy with sentinel lymph node biopsy from the left inguinal area. The pathological examination showed a few isolated metastatic melanoma cells in one lymph node. No tumor was seen in the area of the surgical scar of the previous biopsy.

In December 2015, she was referred to the Oncology Department for evaluation and treatment. Combined positron emission tomography-computed tomography (PET-CT) test showed multiple pulmonary nodules with the largest diameters up to 5 mm in the right upper lobe and right lower lobe as well as “ground glass” shading at the top of the lung. The findings were not felt to represent malignant disease and no other abnormalities were found. The patient was diagnosed and staged as malignant nodular-type ulcerated melanoma of the left thigh, T3b N1mic M0 (stage 3b).

PET-CT in February 2018 showed metastases in the lungs and thoracic spine (vertebrae D10–D11) and lymphadenopathy in the left inguinal area consistent with the diagnosis of metastatic malignant melanoma. We initiated systemic therapy with pembrolizumab 150 mg intravenously every 3 weeks as immunotherapy treatment on February 28, 2018. She was

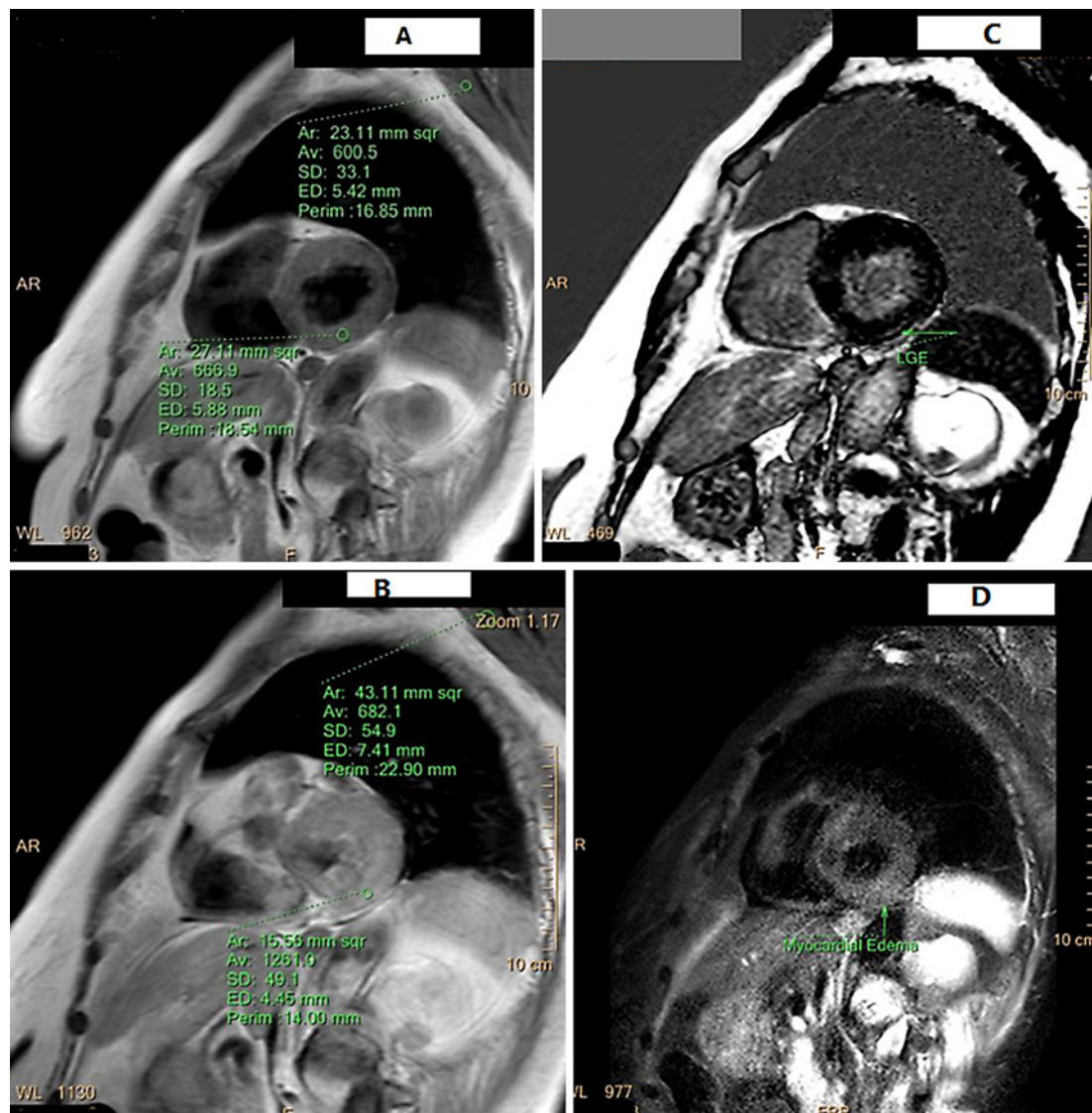


Fig. 1. Myocarditis in patient 1. **A, B** Difference before (**A**) and after (**B**) late gadolinium-enhanced cardiac MRI of the patient, which is a sign of myocarditis (arrow). **C, D** Late gadolinium enhancement in a pattern compatible with myocarditis (injection of gadolinium showing myocardial hyperemia with an area of more pronounced uptake [arrow]).

given palliative radiotherapy to vertebrae D9–L1 (20 Gy, 5 fractions). Orthopedic consultation did not recommend invasive palliative treatment for the spine metastases.

On March 26, 2018, she received the second cycle of pembrolizumab immunotherapy treatment. On April 14, 2018, she was admitted to the Department of Internal Medicine due to chest pain. After 5 days, she was transferred to the intensive care unit due to suspicion of non-ST-segment elevation myocardial infarction with troponin level 490 ng/L (normal 0.0–14.0), which was increasing. Cardiac catheterization demonstrated nonobstructive coronary disease and a hyperdynamic LV function. An echocardiogram was done the same day showing normal LV systolic function with upper septal hypertrophy and elevated LV filling pressure.



Fig. 2. Normal coronary arteries in an angiogram of patient 1.

On April 18, 2018, a cardiac magnetic resonance imaging (MRI) was preformed that demonstrated (Fig. 1) normal LV systolic function with septal hypertrophy. The early gadolinium enhancement (Fig. 1A) ratio was >4 with late gadolinium enhancement (Fig. 1B), in a pattern compatible with myocarditis (Fig. 1C, D).

Corticosteroid therapy was initiated with prednisone 2 mg per kilogram body weight for 1 week, and because of the suspicion that the myocarditis was caused by pembrolizumab, prednisone was continued for 2 weeks at a dose of 1 mg/kg.

Troponin level decreased from 1,103 ng/L to 300 ng/L. Virology testing was performed (hepatitis serology, Q-FEVER phases). DNA PCR for EBV and CMV was negative, HIV was negative, and *Brucella abortus* with Rose Bengal test was not detected.

Two weeks later, she had an echocardiogram that showed normal LV systolic function. An angiogram of the coronary arteries showed normal coronary arteries (Fig. 2).

A multidisciplinary conference including a cardiologist, oncologist, and infectious disease specialist came to the conclusion that the clinical presentation of the patient was consistent with myocarditis as a toxicity of immunotherapy. Pembrolizumab was discontinued.

On May 25, 2018, troponin level was 100 ng/L, and complete blood count and thyroid function were within normal limits. On June 28, 2018, laboratory results showed an elevated troponin level of 131 ng/L, with no other abnormalities. On July 16, 2018, CT of the chest, abdomen, and pelvis showed no vertebral metastasis and no other evidence of metastatic disease.

Between November 8, 2018, and November 12, 2018, she was hospitalized in the Department of Internal Medicine due to high fever (39.5°C) with leukopenia ($2.24 \times 10^3/\mu\text{L}$, normal 4.8–10.8) and neutropenia ($1.4 \times 10^3/\mu\text{L}$, normal 1.9–8).

CT of the total body showed no evidence of the origin of fever with no pulmonary infiltrates or metastases. Urine culture was positive for *Klebsiella pneumoniae*, so she was treated with antibiotics (carbapenem) and discharged home.

From November 25, 2018, to December 3, 2018, while not under active oncology treatment, she was re-admitted to the Internal Medicine Department due to repeated



Fig. 3. Normal coronary arteries in an angiogram of patient 2.

episodes of fever (39.0°C). Blood and urine cultures were negative, as was a panel or serology for viruses (same panel as noted above on April 14, 2018). Echocardiogram showed no abnormalities. On December 4, 2018, CT-PET without injection of contrast material showed no evidence of any infectious process and continued absence of any signs of malignancy.

Case 2

A 55-year-old woman presented in November 2017 with a nevus 14 cm in diameter on the skin of her upper back. The dark blue nevus had been present since birth but recently had become larger and darker in color.

She had received treatment for hypertension and type 2 diabetes mellitus. Past medical history included total thyroidectomy in 2016 for papillary carcinoma of the thyroid and excision of a benign endometrial polyp in 2004. She had no family history of cancer and was not a smoker.

On December 19, 2017, biopsy of the nevus showed metastatic malignant melanoma. She then underwent a total body PET-CT that showed hypermetabolic absorption in the vertebral bodies and soft tissue at levels D5, D7, and D9 (the area of the nevus) with high absorption, consistent with malignant disease.

We initiated systemic immunotherapy with nivolumab 200 mg intravenously every 2 weeks. After the fourth cycle of treatment, she developed itching and mild skin rash. One week later, she was admitted to the Department of Internal Medicine because of headache, weakness, and increase in liver enzymes with GOT (AST) 53 U/L (normal 0–31) and GPT (ALT) 56 U/L (normal 0–34). Further evaluation included chest radiography with no evidence of pathological findings; abdominal ultrasound with no evidence of pathological findings; and CT of the abdomen with no evidence of intra-abdominal metastatic findings.

Complete blood count and chemistries were normal except for the liver enzymes previously noted as elevated, now decreasing. Hepatitis serology was negative. She was discharged home after 10 days.

One week later, repeat PET-CT test was performed, which showed stable disease. At that point, we elected to add Ipilimumab 75 mg and administer it together with the nivolumab 200 mg every 3 weeks.

In May 2018, she received the second cycle of nivolumab plus ipilimumab. Two weeks later, she was admitted to the Department of Internal Medicine with chest pain, fever (38.7°C), and dyspnea. Electrocardiography showed a normal sinus rhythm. Echocardiogram showed normal LV systolic function with an ejection fraction of 65% and signs of impaired LV relaxation with normal LV filling pressure. Right ventricular function was preserved. There was mild mitral regurgitation and no pulmonary hypertension. Angiogram of the coronary arteries showed normal coronary arteries (Fig. 3).

Ventilation/perfusion lung scan was normal; complete blood count and blood chemistries were normal; and troponin level was high, initially 326 ng/L, then decreasing to 256 ng/L. Steroid therapy was initiated (prednisone 1.5 mg/kg). Virology testing showed the following: DNA PCR for EBV and CMV was negative, HIV was negative.

Further investigations showed the following: antinuclear antibody test was negative, anti-neutrophil cytoplasmic antibodies were negative, she had a normal immunoglobulin level, and complete blood count and blood chemistries were normal except for a mild increase in liver enzymes (GOT [AST] 80 U/L, GPT [ALT] 73 U/L) and elevated lactate dehydrogenase (843 U/L, normal 230–480). Blood culture showed no bacterial growth.

CT scan of the spine showed no evidence of metastasis. MRI of the heart showed normal LV systolic function and normal right ventricular systolic function; there was no evidence of myocardial late gadolinium enhancement and there was mild mitral regurgitation as well as minimal pericardial effusion. There were no diagnostic signs of myocarditis, but after consultation with a cardiologist, the diagnosis of myocarditis was made on clinical grounds.

On August 2018, she underwent PET-CT which showed weak hypermetabolic absorption in soft tissue in the area of the nevus. A multidisciplinary conference including an oncologist and a plastic surgeon recommended wide excision of the nevus, which was performed on September 13, 2018. The pathology results showed metastatic melanoma with negative margins.

Two months after the surgery, she was admitted for PET-CT for follow-up, which showed no evidence of disease. Presently, she is receiving nivolumab 200 mg every 2 weeks as adjuvant therapy with no evidence of disease recurrence and normal troponin level.

Discussion and Conclusion

We have described 2 patients each of whom had a rare serious adverse event, myocarditis, known to be caused by ICIs. Both patients went on to have a complete response of widespread metastatic disease to immune therapy. Severe cardiologic side effects with immunotherapy are uncommon but are in most cases reversible; therefore, close follow-up is very important for patients on ICI treatment. We suggest that the occurrence of a severe immune-related toxicity, myocarditis, was predictive of a dramatic tumor response to immune-based therapy.

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Statement of Ethics

All subjects have given their written informed consent to publish their case (including publication of images).

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