Disseminated Melanoma: A Disappearing Left Ventricular Mass

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INTRODUCTION

Intracardiac metastasis is a commonly described manifestation of disseminated melanoma. Data on the incidence of cardiac metastases are limited as most diagnoses are established postmortem given the lack of cardiac symptoms at presentation.[1] Cardiac involvement can include multiple myocardial metastases with large masses involving all 4 chambers of the heart, with the right atrium being the most commonly affected.[1] The intracavitary masses can lead to ventricular outflow or inflow obstruction, arrhythmias, heart failure, heart block, and/or pericardial effusions.[2]

Transthoracic echocardiography (TTE) is one of the initial diagnostic imaging modalities for cardiac tumors given the relative accessibility, low cost, and feasibility. Visualization of these tumors on TTE may prompt further workup with transesophageal echocardiogram, cardiovascular magnetic resonance (CMR) imaging, and positron emission tomography computed tomography (PET-CT).[2] Treatment of cardiac involvement in metastatic melanoma includes a combination of immunotherapy, targeted molecular therapy, and surgical intervention. Surgical excision of cardiac metastases is often discussed as a first-line intervention and is highly dependent on the extent of hemodynamic compromise from the cardiac mass.[2]

We present a patient with metastatic melanoma, highlighting the role of echocardiography in monitoring cardiac metastases over time.

CASE PRESENTATION

A 58-year-old woman with hypothyroidism and neurofibroma of the sciatic nerve presented with right hand weakness and foot drop. Brain magnetic resonance imaging revealed 20 hemorrhagic brain metastases with diffuse parenchymal spread. Further workup with PET-CT revealed a subcutaneous lesion in the right upper back and fluorodeoxyglucose- (FDG-) avid uptake in a subcarinal lymph node and left ventricle of the heart (Figure 1A). Further characterization with CMR revealed a 1.5 × 1.3 cm mass present in the left ventricle attached to the midseptum (Figure 2). The mass had rough edges, had invaded into the septum, and had a heterogenous appearance on perfusion and delayed enhancement imaging (Figure 3). There was extension of the mass into the septum that appeared to be attached by a thin stalk and was mobile. The mass was isointense within the myocardium on T2 weighted imaging and did not suppress on fat saturation (Figure 4). The mass position correlated with the abnormal FDG-avid uptake noted on the PET-CT scan. Left ventricular systolic function was normal, with a calculated ejection fraction of 59%.

The patient denied cardiac symptoms including dyspnea, angina, palpitations, syncope, paroxysmal nocturnal dyspnea, orthopnea, or lower extremity edema. Skin punch biopsy of the subcutaneous lesion on the back confirmed melanoma. Further analysis revealed a mutation in the gene B-Raf (BRAF) V600 E, which is a commonly mutated proto-oncogene within the family of mitogen activated protein kinases in cutaneous melanoma.[3] V600 E refers to a point mutation from valine to glutamate at codon 600 during protein synthesis. The patient completed 2 cycles of immunotherapy with ipilimumab and nivolumab, which are both monoclonal antibodies that bind to cytotoxic T lymphocyte antigen-4[4] and programmed death-1 receptor,[5] respectively. The patient also underwent cardiac radiation therapy.

Follow-up brain magnetic resonance imaging 1 month later revealed an increase in the size of the hemorrhagic brain lesions. Transthoracic echocardiography during this time also revealed an increase in the size of the cardiac mass to 2.5 × 1.3 cm (Figures 5A and 6A, Video 1). There was no evidence of systolic or diastolic dysfunction, arrythmias, heart block, pericardial effusion, or hemodynamically significant left ventricular outflow tract obstruction with serial TTE throughout treatment. The patient remained asymptomatic from a cardiac perspective. Targeted molecular therapy directed at inhibiting the protein kinases in the mitogen activated protein kinases pathway was initiated with encorafenib and binimetinib given worsening metastatic disease on image findings. Encorafenib specifically inhibits BRAF V600 E, and binimetinib inhibits additional protein kinases MEK1 and MEK2.[6]

Surveillance TTE 6 months later revealed complete resolution of the cardiac mass (Figures 5B and 6B, Video 2), which was confirmed by PET-CT (Figure 1B). The patient continued treatment with encorafenib and binimetinib and continued to follow up with yearly TTE

VIDEO HIGHLIGHTS

Video 1: Two-dimensional TTE, parasternal long-axis view, obtained 1 month following initial diagnosis demonstrates the large, heterogenous, highly mobile mass attached to the septum and extending into the left ventricular outflow tract prior to targeted molecular therapy treatment.

Video 2: Two-dimensional TTE, parasternal long-axis view, obtained 6 months following initial diagnosis demonstrates resolution of the mass posttreatment.

View the video content online at www.cvcasejournal.com.

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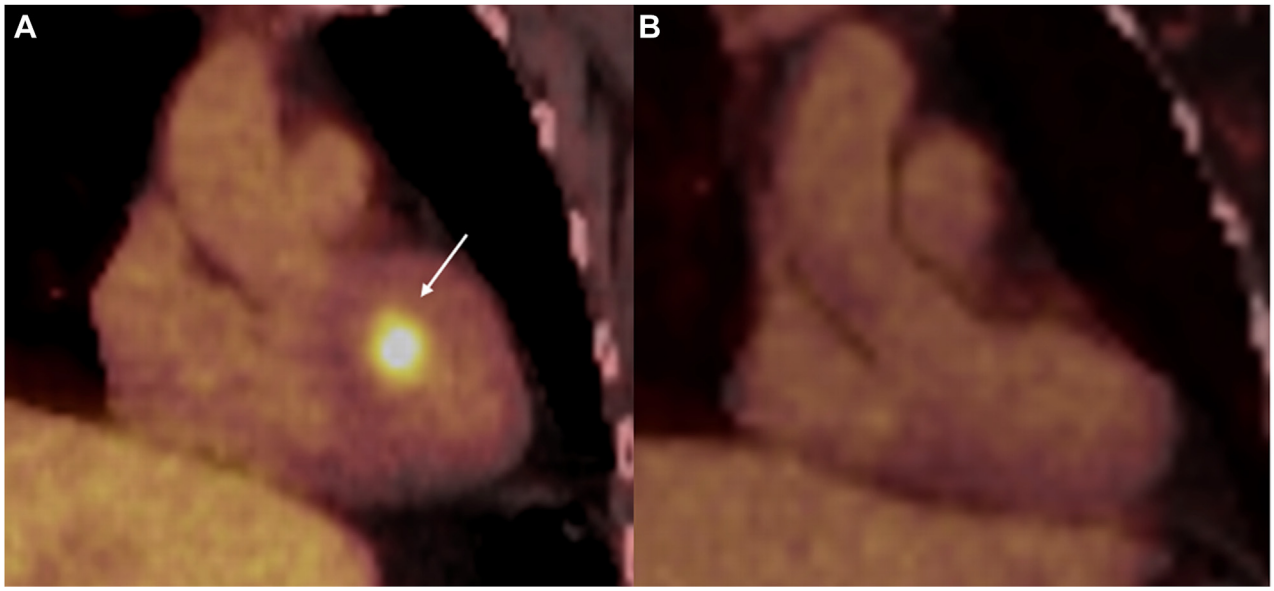

Figure 1 Positron emission tomography–computed tomography FDG scan in coronal plane pre- **(A)** and post- **(B)** treatment. Image shows FDG-avid focus (*arrow*) in the heart with resolution after treatment 6 months following initial diagnosis.

without any evidence for cardiac masses. The brain lesions progressed on follow-up 1 year later resulting in death from brain metastases.

DISCUSSION

Cardiac metastases from melanoma are largely underdiagnosed given the lack of clinical symptoms and are associated with a high rate of mortality.[1,7] Cardiac involvement is often an incidental finding or found during cardiac workup in symptomatic patients. Echocardiography is usually the first-line imaging modality for diagnosis and is used to monitor the response of cardiac tumors to nonsurgical treatment.[8] Further characterization of cardiac metastases includes computed tomography and CMR[2]; however, these studies are expensive and impractical for routine monitoring. Current management following diagnosis includes prompt surgical evaluation, immunotherapy, and targeted molecular therapy.[2,7]

We describe a patient with a progressively increasing cardiac metastatic mass that was likely due to melanoma and resolved with pharmacologic treatment alone. The left ventricular mass was found incidentally on PET-CT scan during the diagnostic workup for identifying the primary source of malignancy. Although TTE is usually the first-line imaging modality, CMR was utilized first during the patient's admission to further characterize the mass. Transthoracic echocardiography was then used to monitor the size and hemodynamics of the mass over time. Myocardial contrast perfusion imaging with ultrasound-enhancing agents has a role in distinguishing a thrombus from a vascular mass; however, this was not performed in this case as the mass had already been comprehensively characterized on

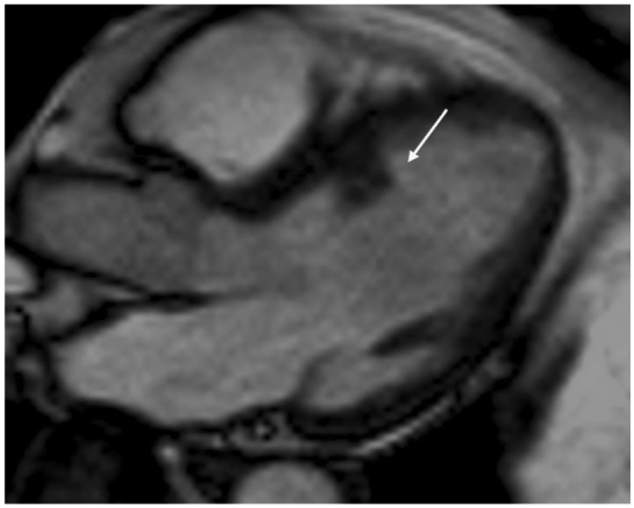

Figure 2 Cine CMR image, steady-state free precession image, diastolic phase, left ventricular outflow tract display, demonstrates a mass (*arrow*) attached to the ventricular septum.

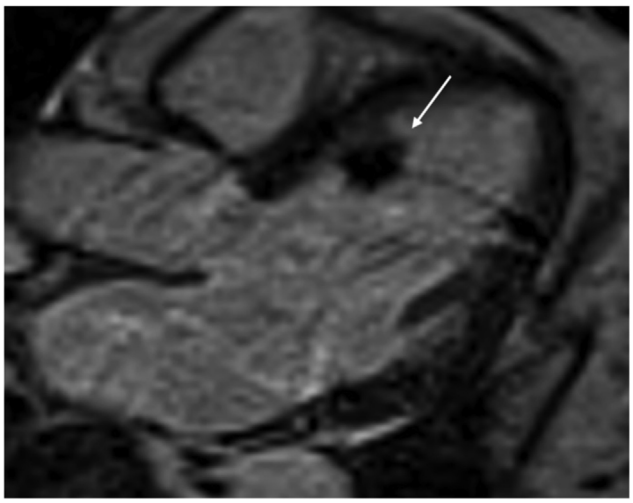

Figure 3 Delayed enhancement CMR image in the left ventricular outflow tract view showing mass (*arrow*) without any enhancement.

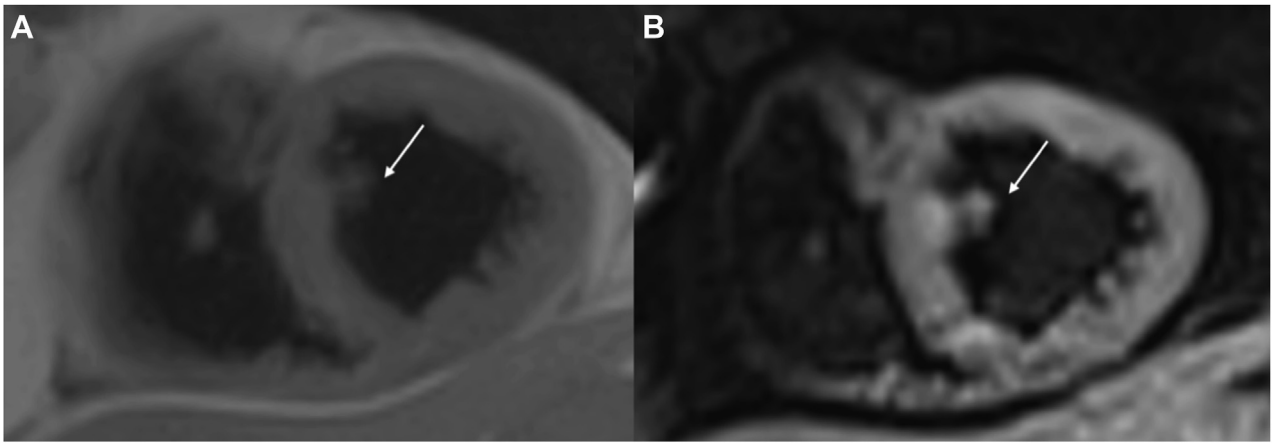

Figure 4 Short-axis CMR images with T2-weighted short Tau inversion recovery images without **(A)** and with **(B)** fat saturation showing the cardiac mass (*arrow*) attached to the septum and infiltrating the septum, which is isointense with the myocardium and does not suppress with fat saturation.

CMR. There was no endomyocardial biopsy to confirm the mass was metastatic disease; however, image findings on CMR and TTE such as septal invasion, rough edges, and heterogenous appearance on perfusion and delayed enhancement imaging made malignancy highly likely.

Treatment of metastatic melanoma has drastically changed over the last 10 years with the expansion of immunotherapy and targeted molecular therapy. First-line treatment usually involves combination immunotherapy with nivolumab and ipilimumab,[9] which has been shown to increase overall survival compared with ipilimumab monotherapy.[10] Localized cardiac radiation therapy is used sparingly due to adverse cardiotoxic effects but has been shown to relieve symptoms and reduce tumor burden.[11] The patient was found to have worsening metastatic disease despite immunotherapy and was then started on targeted molecular therapy with BRAF and MEK inhibitors, encorafenib and binimetinib, respectively. Encorafenib and binimetinib have been shown to improve overall and progression-free survival for patients with metastatic melanoma that have a BRAF-specific mutation.[6,12]

The effectiveness of immunotherapy or targeted molecular therapy in treating cardiac-specific metastases from melanoma is not well studied—largely due to a lack of cardiac workup in patients with melanoma and diagnosis of cardiac involvement postmortem.[1] Additionally, all of the studies showing improved survival with immunotherapy and targeted molecular therapy in metastatic melanoma do not categorize or provide subanalyses for patients with cardiac involvement.[9,10,13] There have been no reports showing complete resolution of a cardiac tumor secondary to melanoma with targeted molecular therapy. Poulsen *et al.*[14] describes a patient with regression of a cardiac melanoma tumor with ipilimumab and nivolumab after 6 weeks of therapy; however, further monitoring was limited by worsening extracardiac metastatic disease, and the patient was not treated with targeted molecular therapy.

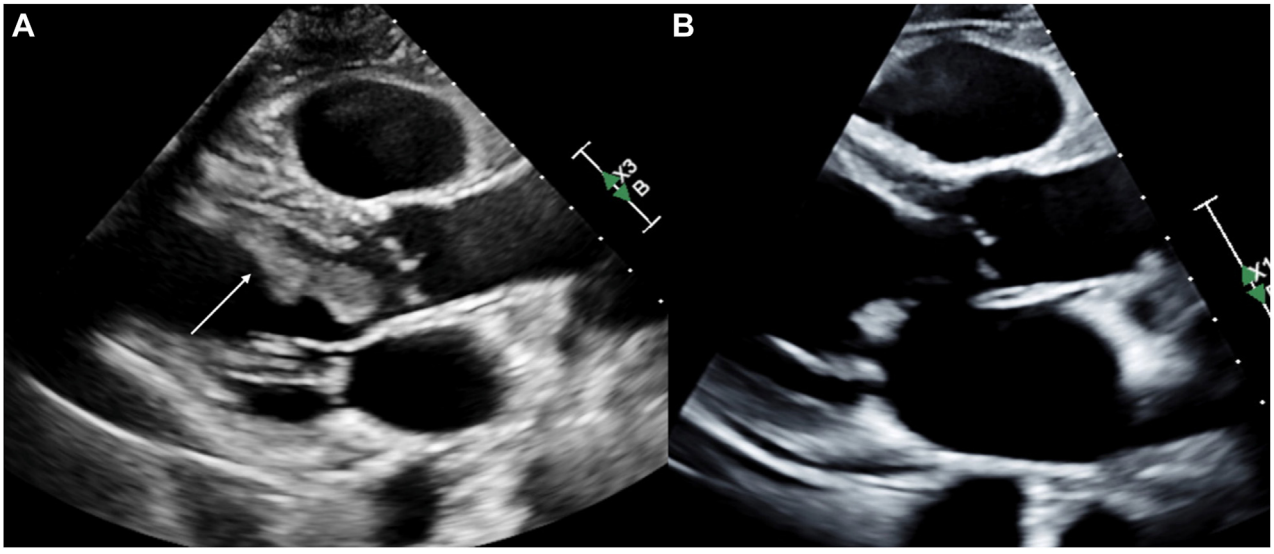

Figure 5 Two-dimensional TTE, parasternal long-axis views, end-diastolic phase, obtained 1 month following initial diagnosis demonstrates the mass (*arrow*) attached to the septum and extending into the left ventricular outflow tract prior to targeted molecular therapy treatment **(A)** and resolution of the mass posttreatment **(B)**.

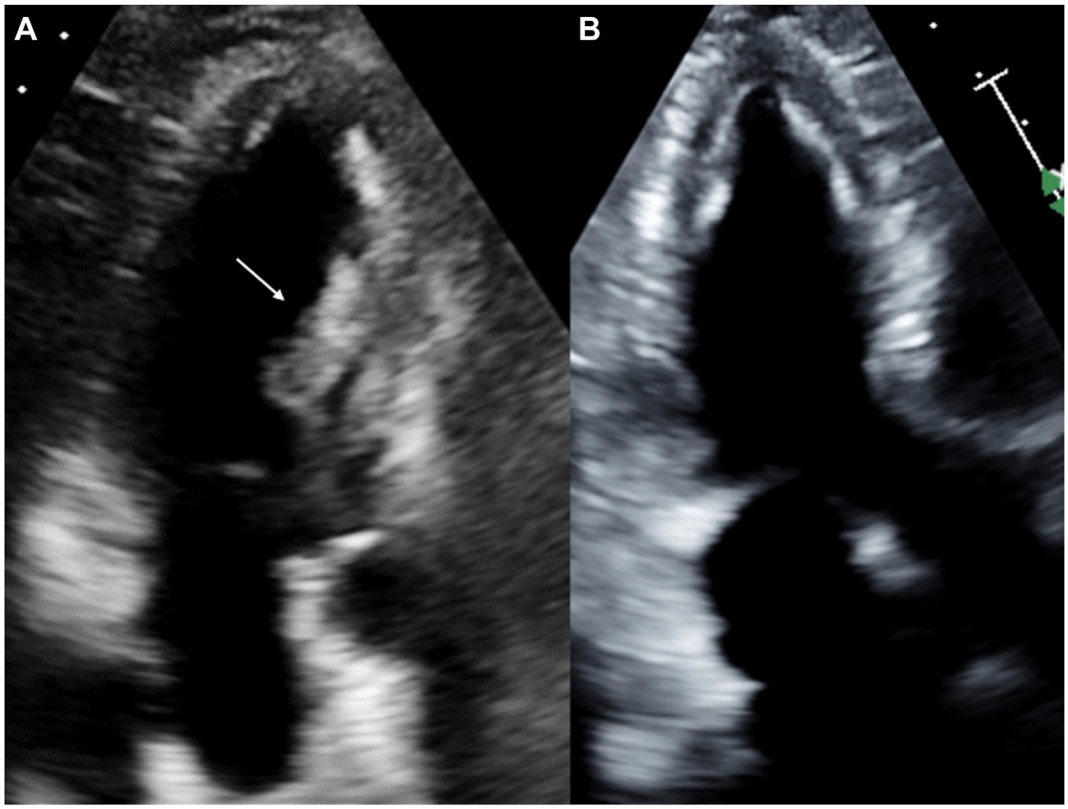

Figure 6 Two-dimensional TTE, apical long-axis views, end-systolic phase, obtained 1 month following initial diagnosis demonstrates the mass (*arrow*) attached to the septum and extending into the left ventricular outflow tract prior to targeted molecular therapy treatment **(A)** and resolution of the mass posttreatment **(B)**.

We are uncertain to what extent cardiac radiation, immunotherapy with ipilimumab and nivolumab, or targeted molecular therapy with encorafenib and binimetinib contributed to the resolution of the left ventricular mass. Image findings suggest the cardiac mass increased in size following treatment with ipilimumab and nivolumab and resolved completely following encorafenib and binimetinib treatment. Embolization of the mass or part of the mass was a consideration throughout the case, and there are reports of silent brain infarcts following various cardiac procedures.[15] While surgical intervention was considered, the patient was deemed too high of a surgical risk given the extent of the intracranial metastases and risk for hemorrhage. Further studies are needed to determine the response of cardiac-specific metastases from melanoma to these therapies.

Although there are several different imaging modalities used to identify cardiac masses, echocardiography is feasible, accessible, and effective in monitoring these metastatic lesions over time. Resolution of cardiac metastatic lesions has significant prognostic value and plays a role in the choice of future management strategies; therefore, close monitoring with echocardiography is crucial and may be utilized in the future to determine response to immunotherapy and targeted molecular therapy.

CONCLUSION

This case is a unique presentation of disseminated melanoma complicated by a left ventricular metastatic mass that resolved in the setting of cardiac radiation, immunotherapy, and targeted molecular therapy. Echocardiography was utilized as the primary imaging modality to monitor the hemodynamic and structural implications of the mass over time. The case highlights the role of echocardiography screening in patients without cardiac symptoms in the setting of disseminated melanoma as well as monitoring the response to treatment in patients with metastatic cardiac involvement.

ETHICS STATEMENT

The authors declare that the work described has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans.

CONSENT STATEMENT

Complete written informed consent was obtained from the patient (or appropriate parent, guardian, or power of attorney) for the publication of this study and accompanying images.

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DISCLOSURE STATEMENT

The authors report no conflict of interest.

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SUPPLEMENTARY DATA

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