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Case Report

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Current diagnosis and management of cardiac melanoma: a case series and review

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Abstract

Malignant melanoma is believed to have the highest rate of cardiac metastasis of any cancer based on autopsy studies, but descriptions of clinical findings, diagnosis, and treatment remain lacking. In particular, the use of immunotherapy has been only sparingly described. We present eight cases of malignant melanoma treated at our institution. Four patients displayed symptoms, three were diagnosed on routine surveillance imaging, and one was diagnosed postmortem. Locations of cardiac tumors varied with all four chambers and septum involved between the cases. Six patients underwent genetic profiling: two patients had a CDKN2A variant detected in their cardiac tumor, one patient had a BRAF mutation, and one patient had an NRAS mutation. Six patients underwent immunotherapy with either anti-PD-1 and/or anti-CTLA-4 therapy. This report highlights the importance of considering cardiac melanoma in surveillance imaging and the use of immunotherapy for management.

Keywords: Melanoma, metastasis, cardiac tumor

INTRODUCTION

Metastases of malignant melanoma occur in up to 30% of cases, but reports of cardiac involvement are rare[1]. While melanoma comprises only 1%-3% of cutaneous tumors in the United States due to its

propensity to metastasize, it accounts for 60% of skin cancer-related deaths[2,3]. Melanoma metastases have been associated with a wide variety of neuroendocrine signaling pathways that disrupt homeostasis[4]. Hematogenous spread commonly results in metastases to the lungs, liver, and brain. Malignant melanoma is believed to have the highest rate of cardiac metastases of any cancer, although cardiac metastases from lung and breast carcinoma remain more common in absolute numbers due to the relatively higher frequency of these cancers in the population[5]. An autopsy study of 70 patients with known metastatic melanoma found cardiac metastases in 64% of cases[6]. However, cardiopulmonary symptoms were present in only 16% of cases, suggesting that clinically silent cardiac involvement is not uncommon. Cardiac melanoma has a poor prognosis with a median survival of 12 to 24 months reported in past case series[7,8].

Clinical findings described in cardiac melanoma have been mixed. Metastases appear to be most common on the right side of the heart but have been described in many locations with various resulting symptom profiles[8,9]. Features of several imaging modalities have been described, including magnetic resonance imaging, echocardiography, and positron emission tomography (PET)[10,11]. For representative images of commonly used imaging modalities in our patient cohort, see Figure 1. While echocardiography is often used to provide preliminary diagnostic information for cardiac tumors and PET scans may aid in identifying metastases in general, CT and MRI scans are most useful for further characterization and tumor demarcation[12]. Cardiac MRI, in particular, provides information on tissue properties such as vascularity that can inform diagnosis[13]. Surgical management is often avoided due to advanced disease and is aimed at amelioration of cardiac symptoms[14,15].

While cases of cardiac melanoma have been described, optimal medical and surgical management has not been fully elucidated. With the advent of newer targeted therapies and checkpoint inhibitors combined with minimally invasive surgical treatment, there may be an opportunity to improve the management of cardiac metastasis. We present eight cases of metastatic melanoma to the heart and describe diagnosis, oncologic and surgical management, and patient course.

CASE REPORT

Electronic medical records of previously identified patients with known diagnoses of melanoma with metastases to the heart between 2012 and 2022 at the Yale-New Haven Hospital were reviewed. Data on patient demographics, clinical notes, treatment plans, pathology reports, genetics reports, imaging reports including MRI, PET/CT, CT, echocardiography, and operative notes were collected.

The records of eight patients were reviewed, including three women (38%) and five men (62%). The median age at first melanoma diagnosis was 67.5 years (Range: 23-81 years). The median time to identification of cardiac involvement was 4 years (Range: 0-15 years). Melanoma first presented with cardiac findings in one case, and cardiac involvement was identified postmortem in one case [Table 1].

Four patients displayed symptoms associated with cardiac metastasis: two with new-onset dyspnea, one with worsened existing dyspnea, and one with new-onset atrial fibrillation. An additional patient had a history of congestive heart failure and pulmonary embolism pre-dating their melanoma diagnosis, and cardiac metastasis was discovered postmortem. The remaining three patients did not display cardiopulmonary symptoms. Three patients had a cardiac mass discovered on surveillance imaging as an incidental finding. Seven of eight patients had at least one other site of metastasis identified including six patients with pulmonary involvement, two with lymph node involvement, two with liver involvement, one with small intestine and adrenal involvement, and one with brain involvement [Table 1]. Biopsy specimens of intracardiac lesions were not uniformly obtained and comparative genetic/histological data is unavailable.

Table 1. Characteristics of patients with cardiac melanoma

Age at diagnosis of melanoma	Age at diagnosis of cardiac metastasis	Gender	Race	Primary lesion location	Cardiac metastasis location	Treatment	Cardiac presentation	Other metastatic sites
80	83	Male	White	Unknown	Intra-atrial septum	Combination ipilimumab and nivolumab followed by nivolumab maintenance therapy and radiation therapy to left hilum/ heart	New atrial fibrillation	Left hilum
79	79	Female	White	Unknown	Left atrium	Nivolumab monotherapy	Dyspnea	Lung
79	81	Male	White	Left great toe	Right ventricle and right ventricular outflow tract	Pembrolizumab	None	Psoas muscles, left thigh muscle, and lung
70	Postmortem*	Male	White	Right calf	Unspecified	N/A	Unclear - history of congestive heart failure and pulmonary embolism pre-date melanoma	Lungs, peritoneum, lymph nodes, heart, small intestine, adrenals, and peripelvic fat
63	67	Male	White	Right neck	Right ventricle	Ipilimumab and nivolumab	None	Lung, liver, right ventricle, right groin, and clivus
65	70	Male	White	Right shoulder	Right atrium (abutting interatrial septum)	Combination ipilimumab and nivolumab followed by nivolumab monotherapy. Received gamma knife radiation therapy for brain metastases	None	Liver, brain, lungs, and ribs
23	38	Female	White	Left arm	Left atrioventricular septum invading into myocardium; malignant pericardial	Adjuvant low-dose interleukin-2 and GM-CSF followed by Vemurafenib	Dyspnea	Scapula
60	66	Female	White	Left medial heel	Malignant pericardial effusion	Topical imiquimod and intralesional IL-2 followed by combined nivolumab and ipilimumab.	Dyspnea	Left inguinal metastases and intra-abdominal lymphadenopathy

*This patient died at the age of 73, 3 years after initial diagnosis.

The location of cardiac melanoma varied in all the patients [Table 1]. Locations included the left ventricular apex, left atrium, tricuspid valve, right ventricle, right atrium, inter-atrial septum, left atrioventricular septum, as well as malignant pericardial effusion. Six patients underwent additional study for genetic profiling and immunohistochemistry staining for PD-1 and PD-L1 on the resected tumor. Tumor mutational panels were used to detect common driver mutations associated with melanoma. Specifically, two patients had CDKN2A mutations, one patient had a BRAFV600E mutation, and one patient had an NRAS mutation. Five patients underwent surgery for primary and/or metastatic melanoma; none had resection of their cardiac lesions, although two patients required pericardial effusion drainage. All patients were also receiving immunotherapy or targeted therapy in conjunction with surgical management. Six patients were treated with immunotherapy with nivolumab (anti-PD-1 therapy) or ipilimumab (anti-CTLA-4 therapy); one patient was deceased before these therapies were approved for use in metastatic melanoma and the other had a discovery of metastasis postmortem. Two patients out of six patients treated with both nivolumab and ipilimumab had complete regression of their cardiac melanoma based on surveillance imaging, while three had progression of their

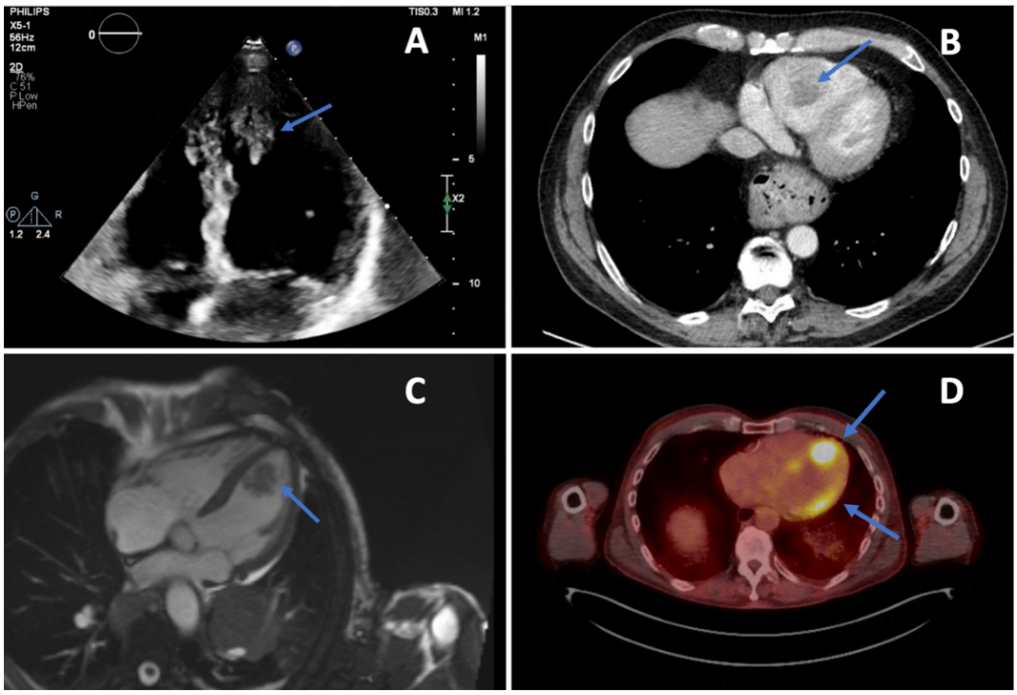

Figure 1. Multiple imaging modalities have been used to detect suspected cardiac melanoma. (A) Echocardiogram showing a 3.1 cm × 2.4 cm mobile echodensity at the apex of the left ventricle concerning for thrombus or tumor. (B) Chest CT showing a 4.3 cm mass in the right ventricle consistent with malignancy. (C) Cardiac T2-weighted MRI displaying a mixed tumor and thrombus at the apex of the left ventricle. (D) PET scan of a hypermetabolic mass at the apex of the left ventricle.

cardiac metastasis. One patient with complete regression of melanoma later developed gastric adenocarcinoma with hepatic metastasis.

DISCUSSION

Cardiac tumors are uncommon, and clinical reports of malignant melanoma with metastasis to the heart are particularly rare[16][Table 2]. Our study examines the management and clinical course of eight patients diagnosed with cardiac melanoma. In general, management was in line with current treatment options available for patients with stage IV melanoma, including combinations of targeted therapy and immunotherapy. Direct surgical management of cardiac tumors was not pursued in these cases.

However, the presence of cardiac metastases postmortem in patients with metastatic melanoma suggests that there is a gap in detection with current surveillance imaging modalities[9]. As techniques and resolution in imaging improve, cardiac metastasis to the endocardium and myocardium should theoretically be better detected. In previously published case series in cardiac melanoma, pericardial or myocardial metastasis was most frequently described, which may indicate a biased detection due to imaging modalities and their sensitivities to detect small metastasis that protrudes into the cardiac cavity[39]. In our cohort of patients, cardiac MRI was used for confirmation of cardiac lesions first seen on other imaging modalities; indeed, cardiac MRI has the capability to differentiate tissues, incorporate multiple imaging planes, and evaluate valve disturbance, which neither echocardiogram nor CT is capable of performing[40]. Though abnormal lesions can be identified with contrast-enhanced CT, a multimodal approach was necessary for accurate localization of the metastasis; the patients studied for this case series had undergone a cardiac MRI to differentiate the lesion along with PET/CT. PET scans have a higher sensitivity and specificity relative to CT scans for detection of all melanoma metastases, but cardiac metastases may be more challenging to detect

Table 2. Literature review of clinical case and retrospective studies of cardiac metastatic melanoma. patients were considered to have received immunotherapy, regardless of whether they began therapy before or after diagnosis

Study	Year	*n*	Age at diagnosis (years)	Sex	Presentation	Location of cardiac metastases	Surgical resection	Immunotherapy
Balinski *et al.*[17]	2022	23	58 (34-105)	13 M, 10 F	Fatigue (35%) dyspnea (30%)	Right ventricle (65%), left ventricle (35%), right atrium (35%)	3 (15%)	13 (57%)
Bortolotti *et al.*[18]	1990	1	49	M	Fatigue, dyspnea	Right atrium	Y	N
Burn *et al.*[19]	2014	1	33	F	Exertional dyspnea	Right atrium	Not reported	Not reported
Canver *et al.*[14]	1990	1	32	M	Fatigue, dyspnea	Left atrium	Y	N
Grazziotin *et al.*[20]	2002	1	64	F	Arterial embolization	Left ventricle	N	N
Kaulen *et al.*[21]	2018	1	80s	M	Unexplained sudden death	All 4 chambers	N	N
Lee *et al.*[22]	2012	1	59	F	Cough	Right atrium	N	N
Liebana *et al.*[23]	2009	1	67	Not reported	Asymptomatic	Right atrium	Not reported	Not reported
Malouf *et al.*[24]	1996	1	73	M	Asymptomatic	Right atrium	N	Y
Messner *et al.*[15]	2003	2	46 (41-50)	1 M, 1 F	Dyspnea, lower extremity swelling	Right ventricle	Y	Not reported
Morosin *et al.*[25]	2019	1	66	Not reported	Not reported	Right atrium	Y	Not reported
Mousseaux *et al.*[11]	1999	4	57 (46-67)	3 M, 1 F	1 cardiac tamponade, 1 superior vena cava syndrome, 2 asymptomatic	Left atrium, left ventricle	1 (25%)	1 (24%)
Onan *et al.*[26]	2010	1	31	M	Heartburn, dyspepsia	Right atrium	Y	N
Ozyunca *et al.*[27]	2006	1	58	M	Complete atrioventricular block	Interventricular and interatrial septum	N	N
Poggi *et al.*[28]	2005	1	41	F	Asymptomatic	Left ventricle	N	N
Poulsen *et al.*[29]	2019	1	65	M	Fatigue, dyspnea	Left ventricle	N	Y
Ramchand *et al.*[30]	2016	1	55	F	Mild cough	Left ventricle	Y	Y
Safa and Olivia[31]	2019	1	61	F	Asymptomatic	Left ventricle	N	Y
Savoia *et al.*[32]	2000	1	53	F	Postmortem	Right atrium and ventricle	N	Y
Spiliopoulus *et al.*[33]	2021	1	71	M	Dyspnea on exertion	Right atrium and ventricle	Y	Y
Tas *et al.*[34]	2010	1	44	F	Asymptomatic	Interatrial septum	N	N
Tesolin *et al.*[35]	2005	1	17	F	Tachycardia	Apical left ventricle	N	N
Thant *et al.*[13]	2021	1	79	F	Atrial flutter, presyncope	Right atrium, interatrial septum	N	Y

Tse *et al.*[7]	2017	11	63 (54-72)	7 M, 3 F	Dyspnea (64%)	5 right atrium (46%), 2 right ventricle (18%), 2 left atrium (18%), 1 left ventricle (9%), 1 pericardium (9%)	10 (91%)	4 (36%)
de Vasconcelos *et al.*[36]	2013	1	39	M	Chest pain, numbness from the waist down	Anterolateral wall of left ventricle	Y	N
Villa *et al.*[37]	2014	1	61	M	Dyspnea, syncope	Interventricular septum, right cardiac apex, right atrial polypoid mass	N	N
Vukicevic *et al.*[38]	2020	1	42	F	Hypotension, dyspnea, tachycardia	Right ventricle and atrium	Y	N
Wood *et al.*[8]	2008	7	60 (31-79)	4 F, 3 M	Dyspnea or substernal pressure	4 right atrium, 2 right ventricle, 1 left ventricle	Either biopsy or Resection	Not reported
Zitzelsberger *et al.*[9]	2017	25	58 (26-89)	12 M, 13 F	Asymptomatic	17 right atrium (67%), 8 right ventricle (33%)	1 (4%)	Not reported

M = male, F = female, Y = yes, N = no.

on this modality due to the typical uptake observed regularly in the heart[41]. In a study of 103 patients, Holder *et al.* found a sensitivity and specificity of 94.2% and 83.3%, respectively, for detection of all melanoma metastases with PET, compared to 55.3% and 84.4% for CT imaging[41]. A recent study by El-Shourbagy *et al.* examining 18 patients similarly found a sensitivity and specificity of 100% and 66.66% for detection of metastases of any location with FDG-PET/CT[42]. A 2019 review of imaging for staging and re-staging of cutaneous melanoma in adults noted that existing literature primarily focuses on PET/CT imaging, while comparative data with MRI and CT imaging are lacking[43].

It has been previously described that the right atrium is the most common site of metastasis[9]. In our series, we had a wide array of cardiac metastatic locations. In a study describing CT imaging of cardiac melanoma in 25 patients, left ventricle and left atrium involvement were described in 17% and 8% of cases, respectively, while in the present series, one case involved the left atrium and one involved the left atrioventricular septum[9]. Other reports of left heart involvement have been rare[8,14].

Surgical management of cardiac tumors in melanoma has been described to palliate symptoms of heart failure and outflow tract obstruction. In the present series, no patients underwent surgery to resect cardiac metastases, given that the majority of the cardiac tumors were asymptomatic. The role of surgical management for cardiac metastases is quite limited and, if pursued, particularly for symptomatic or oligometastatic disease, should be discussed by a multi-disciplinary team.

Treatment of metastatic melanoma to the heart treated with immunotherapy has only been described recently[17,29]. Immunotherapy with either blockade of PD-1 or CTLA-4 therapy is based on activation of cytotoxic T cells to induce an antitumor immune response[44]. The pharmaceuticals, both approved for the treatment of unresectable and metastatic melanoma, function by selectively inhibiting negative regulators of cytotoxic T-cell function to produce a more robust antitumor response. CTLA-4 is believed to regulate the proliferation of T-cells early in the tumor response and decrease regulatory T cells. PD-1 suppresses the later-stage T-cell response in the peripheral tissues[45]. In instances with cardiac metastatic lesions, our institution favors the use of a combination of anti-PD-1 and anti-CTLA-4 therapy because of the improved responses with this regimen. These patients are monitored closely for immune-related adverse events. The heart is mainly thought of as an area of immune privilege, but our series demonstrates that responses can be seen[45]. Interestingly, in these patients, none experienced immune-related myocarditis, highlighting a continued need to understand the specific immune environment of the heart and honing of circulating T cells to this microenvironment. There are currently no available predictors of response to immunotherapy. We observed that 33% of the study patients had a temporary clinical response in their cardiac metastases, but most later developed progression while on immunotherapy. This is consistent with previous papers demonstrating that patients even with PD-L1 positive tumors show resistance or relapse with PD-1 blockade[46,47]. This may demonstrate the need for improved biomarkers in stratifying patients for immunotherapy treatments and assessing the efficacy of combination immunotherapy after initial nonresponse to single-immune checkpoint inhibitor therapy with either anti-CTLA-4 or anti-LAG-3[48]. Targeting different combinations of immune checkpoints may be important for improving response rates and decreasing rates of acquired resistance[49].

This report builds upon others to highlight the importance of considering cardiac involvement in surveillance. This series highlights the need for further research into the utility of surveillance imaging for cardiac melanoma and the potential role of immunotherapy in limiting its progression. While cardiac melanoma should be considered in patients with a history of melanoma who present with new or worsened cardiopulmonary symptoms, half of the patients in this series were asymptomatic. Consideration of cardiac involvement in surveillance imaging may be valuable for improving identification of cardiac metastasis and determining treatment strategies.

DECLARATIONS

Authors' contributions

Conceptualized and designed the study, collected data, drafted the initial manuscript, and revised the manuscript: Long AS, Chang J

Revised the manuscript and generated figures: Glahn JZ

Critically reviewed the manuscript for intellectual content: Tran TT

Conceptualized and designed the study, provided administrative, technical, and material support, and critically reviewed the manuscript for intellectual content: Clune J, Olino K

Availability of data and materials

Not applicable.

Financial support and sponsorship

None.

Conflicts of interest

All authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

This study was deemed exempt from review by the Yale University Institutional Review Board (HIC#2000032566). Individual patient consent was not required.

Consent for publication

This study was reviewed by the Yale Institutional Review Board (HIC#2000032566), which determined that consent was not necessary for publication.

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