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Surgical Management of the Patient with Metastatic Melanoma to the Heart

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Abstract

Melanoma has a high propensity for cardiac seeding, with heart involvement noted in a significant number of patients at autopsy. Therapeutic options are currently limited, and the prognosis of cardiac metastasis is poor. We report two cases of cardiac metastasis of melanoma and review the current literature. In addition we propose an algorithm for dealing with this difficult problem.

Introduction

Melanoma is an aggressive neoplasm with a poor prognosis.. The incidence of melanoma is increasing worldwide at a rate greater than that of any other form of neoplasm.(1) Once metastasis has occurred, median length of survival is 6.4 months.(2) Cardiac involvement in patients with metastatic melanoma is a common finding postmortem and melanoma is known to have a high, if not the highest, propensity for cardiac metastasis of any human neoplasm.(1, 3–8) However it is not often diagnosed. Patients may experience long disease free intervals after initial diagnosis and new cardiac metastasis have been reported more than 20 years after the initial excision of a primary cutaneous lesion.(9–11) We discuss two patients with malignant melanoma who presented with new cardiac metastasis many years after treatment of the primary lesion. Both patients were managed surgically, with short survival, one with previously unreported embolic complications. We discuss the current options for treatment and propose how they may be optimally utilized.

This study qualified for waiver of approval according to local Institutional Review Board policies, thus approval was not sought or necessary.

Case I

A 36 year-old female presented with a Clark's level IV melanoma of the abdomen, 1.4 mm in depth, in June, 2007. She was treated with wide local excision and sentinel lymph node biopsy, which was negative for metastases. Three years later recurrence was discovered in the right axilla and axillary dissection was performed with 2/10 nodes positive. She subsequently enrolled in a clinical trial of a cancer vaccine, but came off-study due to further axillary recurrence treated with surgery, radiation and two courses of high dose interleukin-2 therapy. In 2011, CT revealed an asymptomatic 4.1×5.1 cm right ventricular mass and multiple new lesions throughout her body. She was subsequently enrolled in a clinical trial of ipilimumab during which trans-thoracic echocardiogram (TTE) revealed progression of the intracardiac mass causing significant outflow obstruction (figure 1, A). Later that month she experienced dyspnea on exertion consistent with NYHA III heart failure, thus she was scheduled for resection of the intracardiac lesion. Preoperative trans-esophageal echocardiogram (TEE) found the mass to involve >90% of the right ventricle with prolapse into the right atrium through the tricuspid valve. The metastasis encased the anterior valve leaflet. She underwent right ventricular metastasectomy on cardiopulmonary bypass, with resection of a 7×7×2 cm mass (figure 1, B,C). Repair of the tricuspid valve was also performed, using an Alfieri stitch. Pathology confirmed metastatic melanoma. Two weeks later, she was readmitted with hemorrhage from a necrotic liver lesion, which was embolized angiographically. She began treatment with temozolomide, but was readmitted shortly thereafter with increased ascites in the setting of hepatic failure. Repeat TTE showed significant regrowth of the previously resected ventricular mass producing significant obstruction with severe compromise of the right ventricular functional capacity (figure 1, D). Shortly thereafter she was transitioned to comfort care and expired.

Case II

Discussion

Despite high prevalence in autopsy studies, cardiac metastasis of melanoma is infrequently diagnosed ante-mortem. Cardiac metastasis without further systemic disease is uncommon(12) and symptoms of cardiac involvement are often non-specific or are masked by the symptoms of additional metastasis.(13–15) Histologically myocardial involvement is most common, with valvular involvement being atypical.(13) Right sided lesions predominate (14) Long term survival in those with cardiac metastasis of melanoma is poor with one group reporting survival of as few as 23% of patients for more than 6 months after the diagnosis of any metastatic cardiac lesion.(16)

Accurate clinical imaging is crucial in order to diagnose cardiac metastases and to determine the feasibility of surgical resection without undue disruption of cardiac function. Echocardiogram has proven to be sensitive for cardiac metastasis and TEE is the preferred modality, as TTE misses 50% of right atrial lesions detected by TEE(17). Additional information gleaned from TEE can be critical in operative planning, as in our case where a previously undiagnosed PFO, which was not demonstrated on prior TTE, presented an

additional risk for systemic tumor emboli. To our knowledge this complication of cardiac melanoma resection has not been previously reported, though embolic phenomena causing transient ischemic attacks have been seen as a presenting symptom of cardiac metastasis. (18)

Cardiac MRI represents an alternative imaging modality. In contrast to other cardiac tumors, on MRI metastatic melanoma displays a characteristic signal intensity pattern with hyperintensity of both T1 and T2 weighted images,(15) though this pattern is not always seen. Gadolinium enhancement of metastatic melanoma is nearly uniformly present.(19)

Due to the poor prognosis associated with cardiac metastasis of melanoma, resection has largely been considered palliative, as in our two examples. Resection prior to the onset of symptoms, when tumor burden is less, may result in improved disease control in the heart and improved outcomes and some success has been reported. Numerous groups have reported successful resection of metastatic melanoma from both atria and ventricles (8, 11, 13, 20–24) with few groups reporting any post-operative morbidity (20) and multiple authors reporting improved quality of life with patients alive up to one year after resection of large solitary cardiac lesions.(8, 13, 21, 23) However, overall morbidity and mortality associated with the resection of cardiac metastasis of melanoma is difficult to assess, as there is little longitudinal data available in the current literature. Operative strategies are varied depending on the exact location of the lesion, and have even included ex-vivo resection and auto-transplantation.(25)

Regarding medical therapy for these lesions, prior to 2010, few options existed for the systemic treatment of metastatic melanoma. Dacarbazine (DTIC) has been for many years the only FDA approved agent, with response rates ranging from 15–25% and complete response rates of 5% with short overall duration (3 – 6 months) with few long-term sustained complete responses (1–2%).(26) Multi-agent cytotoxic regimens have failed to demonstrate significant benefit over DTIC alone. (27) Immunotherapy with high-dose IL-2 has provided an alternative therapy in selected patients with objective responses in 15% of patients with complete responses in 6% of patients which are durable to greater than 30 months.(28) Both treatment options are associated with significant toxicities.

Recent advances in targeted immunologic and molecular based therapies have provided a new landscape in the treatment of metastatic melanoma forcing reassessment of many practices in treating these patients. In 2011, the FDA approved two new therapies for metastatic melanoma, ipilimumab and vemurafenib, which have each demonstrated a survival advantage in Phase 3 clinical trials.(29, 30) These agents but differ in key areas such as patient eligibility, time to response, and response durability, all of which may play a role in therapeutic considerations for the patient with cardiac metastasis.

Vemurafenib (PLX4032) is a selective inhibitor of a form of constitutively activated mutant BRAF serine-threonine kinase (BRAF V600E) present in approximately 50% of melanoma. (31) A recent phase 3 trial comparing vemurafenib to dacarbazine in patients with BRAF mutation demonstrated superior median progression free survival in the vemurafenib group (5.3 months compared to 1.6 months).(30) In this study, 48% of patients had objective

confirmed responses with a median time to response of 1.45 months. Only 2 of the 108 patients with confirmed responses had complete response. A major drawback to this therapy is the development of resistance, with a median duration of response of 6.7 months.(32) Ipilimumab in many ways is a complementary therapy to Vemurafenib. Ipilimumab is an anti-CTLA-4 receptor antibody, which serves to block inhibitory downregulatory signals to T-cells, thus promoting T-cell survival and activation. Two randomized phase three trials using ipilimumab in advanced melanoma have demonstrated a survival advantage.(29, 33) In contrast to vemurafenib, response rate is lower (11 – 15%) however responses are more durable with a median duration of response of 19.3 months.(29, 33) Recently, targeted MEK inhibitors and immunotherapy with PD-1 antibodies have also demonstrated promising results, though are currently only available through clinical trials.(34, 35) None of these therapies are yet approved in the adjuvant setting. As an adjunctive therapy, the role of external beam radiation in the management of cardiac seeding of melanoma remains largely undefined, though encouraging results from one report suggest that it may have a role to play in the future,(36) particularly with early lesions that do not cause hemodynamic compromise.

Given these new developments, reassessment of the management of cardiac melanoma metastasis is in order. Without level 1 evidence to guide us, we must rely on sound oncologic principles and use the different characteristics of each treatment to determine the best course of action in each situation. Clearly, patients with impending hemodynamic collapse are optimally managed with urgent surgical resection and clear margins are desirable, if possible. Patients with isolated or disseminated symptomatic lesions that are not an acute threat to life should undergo BRAF mutation testing. In patients with BRAF mutation, BRAF inhibitors have shown a high rate of response with a short median time to response, thus may result in regression of symptomatic lesions. This may offer the further benefit of converting previously unresectable lesions into those that are amenable to surgical therapy.

For asymptomatic patients with isolated cardiac metastasis in whom resection would render them with no evidence of disease, surgical resection is a reasonable treatment option, if possible. If surgical resection to clear margins does not appear feasible, or if there is evidence of further systemic disease not amenable to resection, ipilimumab should be considered first line therapy, particularly in patients with BRAF wild type melanoma, given the longer durability of disease control.

Regarding the patients described in this report, the first suffered a poor outcome and unfortunately did not respond to treatment with ipilimumab, but may have benefitted from a trial of vemurafenib when she became symptomatic, had BRAF inhibitors been available to her and had she been found to have a BRAF mutation. Our second patient suffered an unfortunate but rare complication of surgical resection, however may have benefitted from earlier surgical resection given the isolated nature of his cardiac disease at the time. With proliferation of new and promising systemic therapies, the outlook for patients with this difficult problem is improving, and surgery will remain an integral part of treatment for patients with cardiac melanoma metastasis.

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Figure 1.

Selected Echocardiographic Images and Photographs from Case One

A: Pre-operative TTE demonstrating tumor filling the right ventricle

B: Intraoperative photograph demonstrating tumor in the right ventricle

C: Gross image of resected cardiac melanoma

D: TTE demonstrating significant tumor regrowth

LV-left ventricle, RA- right atrium, RV- right ventricle

Figure 2.

Selected Echocardiographic and Cardiac MRI Images from Case Two

A: Cardiac MRI demonstrating tumor burden in both atria

B: Cardiac MRI demonstrating tumor burden

C: Intraoperative TEE demonstrating flow through a PFO

D: Intraoperative TEE demonstrating tumor extension through a PFO

LA- left atrium, RA- right atrium