

Cardiac Involvement in Melanoma: A Review of Clinical Manifestations and Management Strategies

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ABSTRACT

Cardiac involvement in melanoma, while clinically uncommon, presents significant diagnostic and therapeutic challenges due to its often silent course and nonspecific manifestations. Melanoma, a highly metastatic skin cancer, can spread to the heart, often remaining asymptomatic until advanced stages, when it may cause nonspecific symptoms such as chest pain and arrhythmias. This review explores the epidemiology, pathophysiology, and clinical manifestations of melanoma-related cardiac metastases, emphasizing the importance of advanced imaging techniques for early detection. It also discusses current management strategies, including immunotherapy and targeted therapies, which have improved survival outcomes. However, despite these advances, the prognosis for patients with cardiac metastases remains poor, highlighting the need for further research into more effective treatments.

KEYWORDS

Melanoma, Cardiac metastases

1 | INTRODUCTION

The skin, derived from the neuroectoderm and mesoderm, is the human body's largest organ and is where cancer can arise from all three layers (i.e., epidermis, dermis, and hypodermis). Indeed, exposure to ultraviolet radiation and a variety of environmental carcinogens can lead to genetic damage and increases the

risk of skin cancer (both melanoma and nonmelanoma). Melanoma is the more aggressive and lethal type of skin cancer because of the increased likelihood for metastasis. (1) Despite extensive investigations into cutaneous manifestations and distant organ metastases, the cardiac implications of malignant melanoma have received relatively limited attention and remain largely uncharted. Furthermore, the incidence of malignant melanoma con-

tinues to rise. (1) While the skin, brain, liver, bone, and intestine are the primary locations of distant metastases in melanoma, it may also affect the heart and present in various ways. (2,3) Secondary cardiac metastases are more common than primary cardiac tumours. (4) Several imaging techniques are crucial in promptly identifying and characterizing heart metastases. Managing these cardiac manifestations often requires surgical procedures or systemic treatments, marking a significant advancement in caring for advanced melanoma patients.

Understanding how melanoma involves the heart is critical for timely diagnosis and appropriate management. Cardiac metastases in melanoma are associated with worse survival, yet they are frequently missed during life and are most often identified only at autopsy. In a review by Tyebally et al. (2020), patients with cardiac metastases demonstrated markedly higher two-year mortality rates compared to those without cardiac involvement (59% vs. 37%; $p = 0.034$), with a median survival of 1.2 years versus 4.4 years, respectively. (5) Management may also differ when cardiac metastases are diagnosed antemortem since treatment must address both the primary malignancy and symptoms arising from cardiac involvement. In one study, 48% of patients experienced at least one cardiovascular complication within the first year following diagnosis of metastatic melanoma. Treatment strategies for cardiac metastases may include immunotherapy (65%), targeted therapy (35%), radiation therapy (25%), and, in some cases, surgical intervention (15%). (6) This review outlines the epidemiology, presentation, imaging techniques, histopathology, and surgical and medical treatments for melanoma that has spread to the heart. While imaging modalities and treatments rapidly evolve, this article aims to provide an updated review.

2 | EPIDEMIOLOGY

The incidence of malignant melanoma has been steadily rising in developed countries over the past few decades, with an estimated 77 230 new cases and over 8 000 deaths in the United States in 2020 alone. (7) In Canada,

an estimated 11 300 new cases of melanoma were reported in 2024, with 1 300 deaths—a 17% increase from 2023. Ultraviolet (UV) radiation remains the primary risk factor, accounting for approximately 85% of melanomas in Canadians over age 30. (8) Although the incidence continues to rise, survival rates in the United States have increased significantly in the past decade, which can be attributed to the development of new targeted immunotherapies. (7) While the 5-year survival rate for patients diagnosed with stage I or II melanoma exceeds 99%, those presenting with distant metastases at diagnosis have a much lower 5-year survival, currently estimated at approximately 35%. (9, 10) Among various malignancies, malignant melanoma has the highest rate of metastasis to the heart. (11) In an autopsy series of 70 patients with metastatic malignant melanoma, cardiac involvement was seen in 64% of patients. (12) Within the group of 70 patients, only 16% had clinically significant cardiac dysfunction while alive. A malignant tumour in the heart did not lead to dysfunction unless there was considerable involvement. (12) Additionally, metastases to the heart may be undetected for over 20 years after the primary cutaneous melanoma diagnosis and excision. (13) Although predating the widespread use of immunotherapy, one study demonstrated that 23% of patients survive beyond six months following the diagnosis of any metastatic cardiac lesion. (5)

3 | PATHOPHYSIOLOGY

Melanoma is a type of cancer originating from pigment-producing cells called melanocytes, which undergo malignant transformation. As melanocytes are produced from neural crest-derived cells, melanomas, although primarily found in the basal layer of the epidermis, can develop and migrate elsewhere including the heart. (14) The pathology of cardiac melanoma remains challenging due to its rarity and the complex nature of the disease. In general, malignant tumours can reach the heart via four main routes: hematogenous spread, lymphatic dissemination, transvenous extension, or direct invasion from adjacent structures such as the lungs or mediastinum. In the case of melanoma, hematogenous

spread predominates, allowing circulating tumour cells to enter the bloodstream and seed distant organs, including the heart. (15) Once in circulation, melanoma cells can adhere to the endothelium and infiltrate cardiac tissue. This mechanism enables tumour cells to lodge within the myocardium or endocardium, sometimes resulting in intracavitary masses. (16) Cardiac metastases from melanoma can involve all three layers of the heart wall and are most frequently observed in the pericardium (69.4%), followed by the epicardium (34.2%), myocardium (31.8%), and endocardium (5%). (17) Moreover, the right atrium is the most common location for melanoma-originating cardiac metastases, and intracavitary tumours are thought to occur via metastasis through the inferior vena cava. Metastases to the left side of the heart are thought to be associated with pulmonary embolism due to the pulmonary circulation and the increased vascularization and mass of the left myocardium. (6) Additionally, metastasis to the valves rarely occurs. (11)

4 | CLINICAL PRESENTATION AND DIAGNOSTIC APPROACH

Cardiac metastases often remain asymptomatic until they grow large enough to physically interfere with heart function, causing what is known as a mass effect. Patients may initially experience nonspecific signs and symptoms, including but not limited to chest pain, palpitations, dyspnea, pericardial effusion, superior vena cava syndrome, dysrhythmias, congestive heart failure, and right ventricular outflow and inflow obstruction. (6, 11) However, in many instances, clinical features such as tachycardia, dyspnea, and anasarca are attributed to non-cardiac involvement of metastatic melanoma, which is explained by the fact that most of the cardiac metastases are relatively small. Cardiac function is only impaired in approximately 30% of patients with cardiac metastases. (4) The nonspecific nature of cardiac metastases and their relatively small size pose a significant challenge for early diagnosis and are often only found at autopsy. Indeed, greater than 50% of patients with metastatic melanoma will have cardiac in-

volvement as proven postmortem. (6) Detection and diagnosis prior to death occur in less than 2% of patients. (6) For all the above reasons, non-invasive imaging techniques play a pivotal role in the early detection of cardiac involvement. Electrocardiography (ECG), however, remains a limited diagnostic tool for identifying cardiac metastases from melanoma due to its nonspecific findings. (11) While ECG changes may occasionally be the first indication of cardiac involvement, most alterations are not unique to cardiac tumours. These abnormalities can result from tumour infiltration, pericardial effusion, or coexisting cardiac conditions, making it difficult to distinguish metastatic involvement based solely on ECG. As highlighted in studies by Hanfling (1960) and Harvey (1968), there are no pathognomonic ECG patterns for cardiac metastases, underscoring the need for more specific imaging modalities for accurate diagnosis. (18, 19) Magnetic resonance imaging (MRI) and computed tomography (CT) have proven to be eligible diagnostic imaging tools as they offer a larger scan size, allowing for full analysis of the chest and identification of any metastases. Furthermore, imaging lung tissue pleura and blood vessels surrounding or entering the heart is important in identifying any metastases invading the heart. While both MRI and CT offer an adequate field of view, contrast resolution and signal intensities in MRI are helpful in differentiating between healthy tissue and cancerous tissue by their characteristic brightness on T1-weighted images. (4)

Regarding histological diagnosis, ultrasound-guided transvenous biopsy is a safe and adequate method of obtaining tissue for diagnostic study compared to a thoracotomy. (14) Histopathological examination reveals distinctive features that include melanin granules, epithelioid or spindle-shaped cells, and the expression of melanoma-associated markers (e.g., S100 and Melan-A). (20) Furthermore, cytological examination of pericardial fluids may also be done, but it was shown to be non-diagnostic in many instances, with only 44-65% of suspected malignant pericardial effusions. (21) Differentiating primary cardiac tumours metastases from and metastases from other primary cancers is of utmost impor-

Disease presentation	Treatment Options
Asymptomatic, solitary lesion	Surgery if complete resection possible
Multiple lesions/systemic disease	Immunotherapy (PD-1/CTLA-4) and/or targeted therapy (BRAF+)
Non-severe symptomatic, BRAF+	Targeted therapy to reduce tumour size, possible surgery later
Severe symptoms, unstable	Urgent surgical resection if feasible
Pericardial effusion	Pericardial drainage if feasible
Chemotherapy	Not first-line and for refractory cases only

TABLE 1 Cardiac Involvement in Melanoma Treatment

tance and requires the expertise of a skilled pathologist.

5 | MANAGEMENT

Management of cardiac manifestations in malignant melanoma necessitates a multidisciplinary approach. The specific intervention depends on several factors, including the location and extent of cardiac involvement, the patient's comorbidities and performance status, and the molecular characteristics of the melanoma. Surgical interventions, such as excision of cardiac metastases or pericardial drainage, may be considered in select cases. (7) The management of cardiac metastatic melanoma should be tailored to each patient's clinical and tumour characteristics. In asymptomatic individuals with a solitary cardiac metastasis, surgery may be a reasonable first-line option if complete resection with clear margins is feasible and would result in no residual disease. Surgical excision is often prioritized when the tumour causes significant hemodynamic compromise. For patients experiencing hemodynamic instability, urgent surgical resection with margins of healthy tissue is recommended, provided the patient's overall condition permits. (22) However, in most cases, cardiac metastasis occurs in the context of widespread metastatic melanoma, which limits the feasibility and curative potential of surgery. As such, surgery is rarely curative but may still be offered to alleviate mass effect or prevent cardiovascular complications, particularly in patients with limited systemic involvement or indolent disease progression. In these

cases, surgery is often used in conjunction with systemic therapy or delayed as part of a salvage approach once disease burden is reduced (Table 1). (23)

Indeed, the advent of **immunotherapy and targeted therapy** has revolutionized the management of advanced melanoma, leading to a dramatic improvement in 5-year survival rates compared with conventional chemotherapy. (24) Consequently, chemotherapy is generally no longer used as first-line treatment in metastatic melanoma. Just ten years ago, metastatic melanoma was almost universally lethal, with an overall 5-year survival rate of approximately 5%. According to the American Cancer Society, the current 5-year survival rate for metastatic melanoma is approximately 35%, reflecting significant improvements. (10) Recent advances in targeted therapies suggest that all patients with metastatic melanoma should be evaluated for BRAF and MEK mutations, especially given that BRAF genes are found in half of melanoma cases, and that anti-BRAF and anti-MEK therapies, such as vemurafenib and cobimetinib, can be offered to patients with improved response. (25) Vemurafenib, a selective BRAF inhibitor, was shown to have a positive response in over 60% of patients with metastatic melanoma as demonstrated by regression in tumour size, survival benefits, and better response time compared to chemotherapy agents such as dacarbazine. (26) Furthermore, immune checkpoint blockade such as PD-1 blocking antibodies (i.e., nivolumab/pembrolizumab) as well as CTLA-4

Stage	Main Treatment Options
Stage 0	• Surgery
Stage I	• Surgery with or without Lymph Node Mapping/Biopsy
Stage II	• Surgery with or without Lymph Node Mapping/Biopsy, Adjuvant Immunotherapy (e.g., pembrolizumab)
Stage III (resectable)	• Surgery • Adjuvant Immunotherapy (nivolumab, pembrolizumab) • Targeted Therapy if BRAF/MEK+
Stage III (unresectable)	• Immunotherapy • Targeted Therapy (if BRAF/MEK+) • Radiation • Chemotherapy (rare)
Stage IV	• Immunotherapy (PD-1: nivolumab/pembrolizumab, CTLA-4: ipilimumab) • Targeted Therapy (BRAF/MEK+) • Radiation or Surgery (palliative)
Recurrent	• <i>Similar to Stage IV: systemic therapy preferred</i> • May include surgery for symptom relief

TABLE 2 Overview of Melanoma Treatments

blocking antibodies (i.e., ipilimumab) have shown significantly improved survival and durable responses in patients with advanced melanoma (Table 2). (27,28)

6 | CONCLUSION

Cardiac metastases originating from melanoma are under-researched, and treatment options remain underdeveloped. Melanoma is a major cause of cardiac metastases. Cardiac metastases from melanoma can be found in all three layers of the heart, whereas non-melanoma cardiac metastases tend to affect the pericardium. Diagnostic tools include ECG, CT, and MRI, with MRI being the most effective option. Currently, there is no consensus on the best treatment plan; however, immunotherapy is the most employed treatment option. Immune checkpoint inhibitors, such as PD-1 and CTLA-4 inhibitors, have improved response and survival rates in patients with advanced melanoma. These treatments are considered the standard of care. In fact, due to their effectiveness, chemotherapy is no longer recommended to treat metastatic melanoma. Non-curative surgeries, such as conservative excisions of car-

diac tumours, are performed solely to alleviate symptoms and enhance quality of life. Despite the global rise in melanoma incidence and meaningful prognostic advances achieved with modern immunotherapy, outcomes for patients with cardiac metastases remain poor. The significant prevalence of cardiac involvement in advanced melanoma, coupled with its association with low survival rates and frequent late detection, represents a clinically significant yet underrecognized problem that warrants greater research focus and dedicated investigation.

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