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CASE REPORT
Cardiovascular imaging

Unresectable cardiac metastasis from melanoma responds well to combination immunotherapy—a case report

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Background Melanoma can metastasize to distal organs including the heart although presentation with a symptomatic cardiac metastasis is rare. The optimal management remains uncertain particularly in the era of immunotherapy.

Case summary We report a case presenting with a large unresectable cardiac metastasis from melanoma that responded well to treatment with immunotherapy.

Conclusion Melanoma can metastasize to the heart and is often challenging to diagnose. Combination immunotherapy can be an effective treatment option even in the setting of a symptomatic and unresectable cardiac metastasis.

Keywords Metastatic melanoma • Cardiac metastasis • Immunotherapy • Case report

ESC curriculum 2.2 Echocardiography • 2.3 Cardiac magnetic resonance • 2.5 Nuclear techniques • 6.8 Cardiac tumours

Learning points

- Melanoma can metastasize to the heart and is most reliably diagnosed with multiple imaging modalities that include echocardiography and cardiac magnetic resonance imaging.
- Combination immunotherapy can be an effective treatment option even for unresectable cardiac metastasis, and recovery of cardiac function can occur with treatment response.
- Phase III trial data for the use of ipilimumab and nivolumab in the setting of advanced melanoma have continued to show durable responses to treatment associated with a significant overall survival benefit.

Introduction

Melanoma is an aggressive skin malignancy with the propensity to metastasize to distant organs, including the heart.[1] We present an unusual case of a patient with a symptomatic large pericardial metastasis as the presenting manifestation of metastatic melanoma. This responded to treatment with immunotherapy with recovery of cardiac function.

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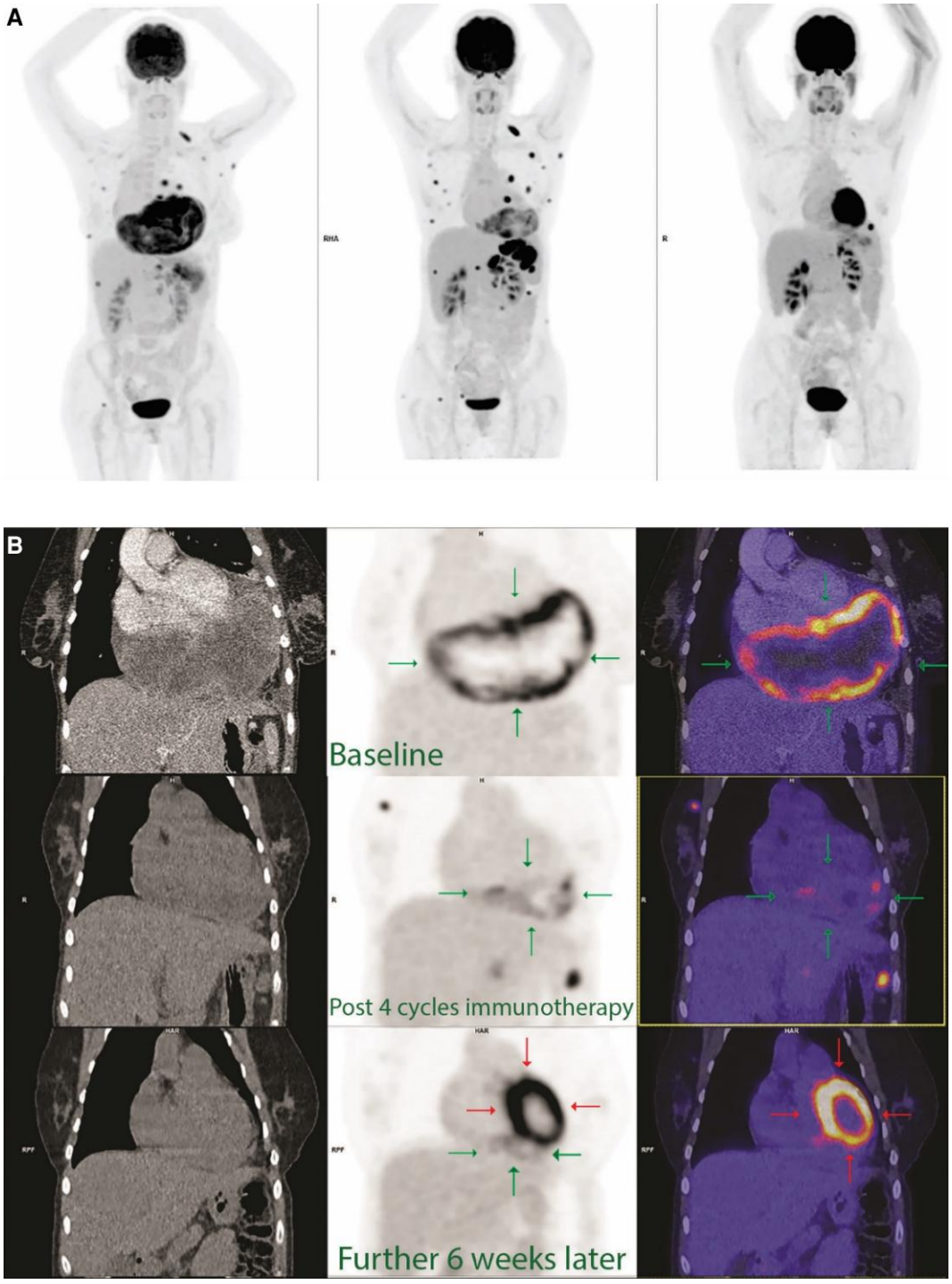
Summary figure



(*A*) Three-time-point whole-body positron emission tomography images at baseline, post-four cycles of induction immunotherapy, and 6 weeks later (from left to right). (*B*) Three-time-point positron emission tomography–computed tomography images showing the large fluorodeoxyglucose cardiac mass (marked with green arrows) at baseline (top row), significantly improved following four cycles of induction immunotherapy (middle row), and almost completely resolved 6 weeks later (bottom row). Note the concentric normal physiologic left ventricular cardiac fluorodeoxyglucose uptake in the most recent scan (bottom row, marked with red arrows).

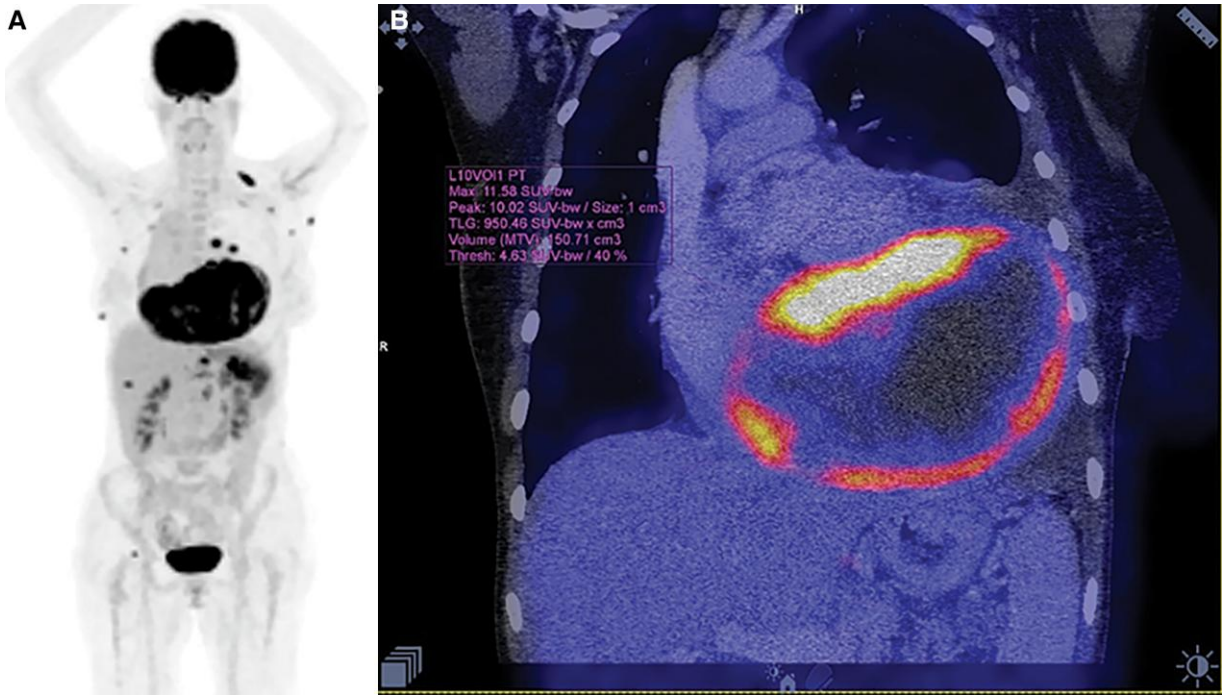


Figure 1 (*A*) Baseline whole-body positron emission tomography. (*B*) Baseline fused positron emission tomography/computed tomography image demonstrating the cardiac metastasis in the coronal plane.

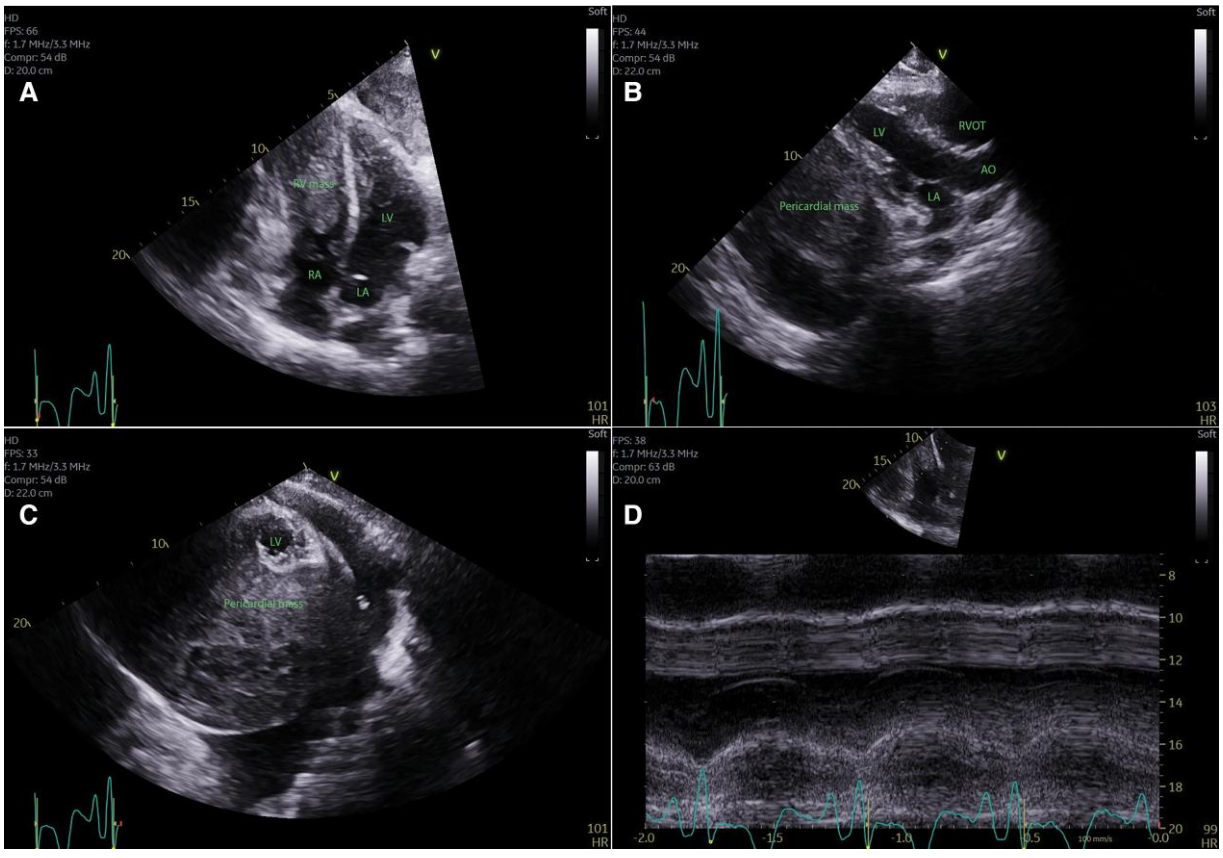


Figure 2 (*A*) Baseline apical four-chamber view on transthoracic echocardiogram. LA, left atrium; LV, left ventricle; RA, right atrium; RV mass, right ventricle with intracavitary mass. (*B*) Baseline parasternal long-axis view on transthoracic echocardiogram. LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract; AO, aorta. (*C*) Baseline parasternal short-axis view on transthoracic echocardiogram. LV, left ventricle. (*D*) Baseline tricuspid annular plane systolic excursion measurement of 12 mm.

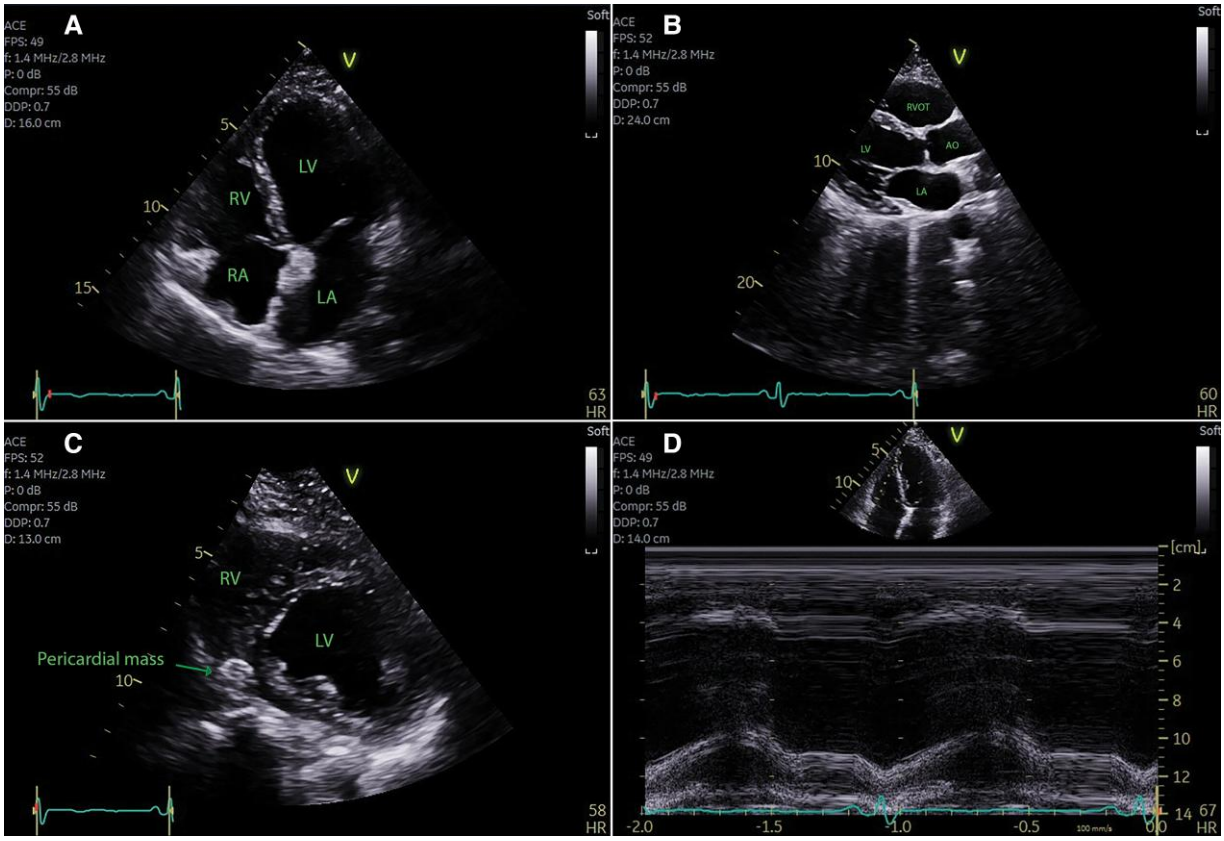


Figure 3 (*A*) Apical four-chamber view on transthoracic echocardiogram following three cycles of immunotherapy. LA, left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle. (*B*) Parasternal long-axis view on transthoracic echocardiogram following three cycles of immunotherapy. LA, left atrium; LV, left ventricle; RVOT, right ventricular outflow tract; AO, aorta. (*C*) Parasternal short-axis view on transthoracic echocardiogram following three cycles of immunotherapy. LV, left ventricle; RV, right ventricle. (*D*) Tricuspid annular plane systolic excursion measurement of 22 mm following three cycles of immunotherapy.

Clinical background

A 51-year-old woman with no remarkable medical history, including any prior primary skin cancers, presented with a 5-month history of worsening exertional dyspnoea New York Heart Association (NYHA) class II. Physical examination revealed supraclavicular lymphadenopathy with no skin lesions noted. Apart from tachycardia, the cardiovascular examination was unremarkable. Baseline electrocardiogram showed sinus rhythm at 104 beats per minute with no other adverse findings.

Whole-body computed tomography (CT) revealed a 14 × 12.5 cm pericardial mass potentially infiltrating the right ventricular (RV) free wall. Further lesions were noted in the lungs and spleen, with extensive nodal and subcutaneous deposits, with uncertainty as to the primary lesion.

Additionally, staging with fluorodeoxyglucose–positron emission tomography (18F-FDG-PET) showed high FDG uptake in the large pericardial mass (SUVmax 11.6), with areas of photopenic central necrosis. There were also FDG-avid metastases in the lung, spleen, lymph nodes, and subcutaneous tissue (*Figure 1A* and *B*), and magnetic resonance imaging (MRI) revealed multiple brain metastases.

Evaluation with transthoracic echocardiography (TTE) (*Figure 2A–C*) showed a large echogenic mass occupying most of the RV cavity associated with impaired RV systolic function. Right ventricular systolic excursion velocity was 6 cm/s, and radial function was severely impaired. This was consistent with tumour infiltration with a differential diagnosis of an RV thrombus. Left ventricular function was intact with concentric remodelling. A baseline cardiac MRI was requested but not performed in time due to the critical disease burden necessitating urgent treatment.

A core biopsy of a right flank subcutaneous lesion confirmed metastatic melanoma, and molecular testing revealed NRAS, TERT promoter, and CDH1 variants. BRAF was wild type, and PD-L1 testing was not performed. Baseline laboratory testing revealed intact organ function with an elevated lactate dehydrogenase (LDH) of 305 U/L (reference range 120–250 U/L). Baseline NT-proBNP was significantly elevated at 3046 ng/L (reference range <100 ng/L), though baseline troponin was not performed.

Paroxysmal atrial fibrillation with rapid ventricular response was diagnosed shortly after the initial presentation and was managed with bisoprolol and amiodarone. Troponin testing performed at this time was within normal limits. Anticoagulation was considered for both atrial fibrillation and the differential diagnosis of an RV thrombus but was ultimately not pursued due to the potential for RV rupture given infiltration of the RV-free wall and the risk of bleeding from intracranial metastasis.

Surgical opinion was sought; however, due to the size and extent of the pericardial mass, surgical excision could not be safely performed. The patient was thus commenced on a combination of ipilimumab (3 mg/kg) and nivolumab (1 mg/kg) immunotherapy given every 3 weeks. Following cycle one of induction treatment, the patient developed a grade three immune-related skin rash that responded to a short weaning course of oral prednisolone. The patient was then successfully

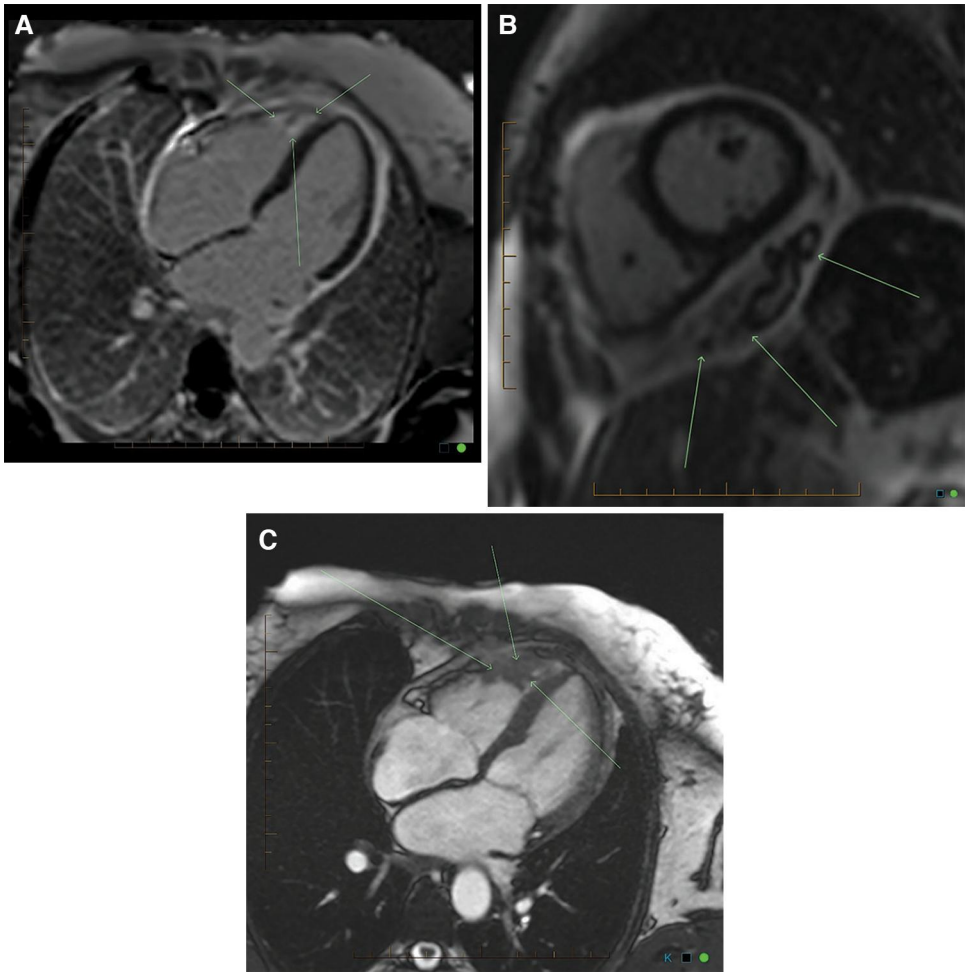


Figure 4 (*A*) Axial cardiac magnetic resonance imaging view with late gadolinium enhancement at the right ventricular apex and pericardium post-four cycles of induction immunotherapy. (*B*) Short-axis oblique views on magnetic resonance imaging with late gadolinium enhancement and heterogeneity of the pericardial tumour post-four cycles of induction immunotherapy. (C) Axial cardiac magnetic resonance imaging steady-state free precession view demonstrating right ventricular filling defect post-four cycles of induction immunotherapy.

rechallenged with combination immunotherapy two weeks later and completed four cycles of induction treatment without further issues.

Repeat TTE following the third treatment cycle (*Figure 3A–C*) showed an almost complete resolution of the pericardial mass. This was associated with good recovery in RV systolic function as evidenced by the tricuspid annular plane systolic excursion (TAPSE) measuring 12 mm at baseline and improving to 22 mm post-immunotherapy (*Figures 2D* and *3D*). Cardiac MRI (*Figure 4A–C*) also showed a significant response in the pericardial tumour (compared with prior CT imaging). The patient's cardiac symptoms resolved, and the patient could perform regular exercise without limitation (NYHA Class I).

Following the fourth treatment cycle, PET imaging showed significant improvement in the pericardial disease (*Figure 5A* and *B*), with mixed responses elsewhere potentially representing pseudo-progression.[2] A repeat MRI head demonstrated progression of intracranial metastasis that was managed with stereotactic radiosurgery. A short interval PET imaging performed 6 weeks later revealed marked metabolic improvement at all sites of disease except for a site of peritoneal disease that remained intensely FDG-avid. The patient continues on maintenance nivolumab 480 mg, given every 4 weeks at this time.

Discussion

As evidenced in this case report, melanoma can metastasize to the heart and this most frequently occurs through haematogenous spread.[3] The most common sites of cardiac involvement are the left ventricle, right atrium, and right ventricle, although varying rates of involvement have been reported.[4] Though the 18-FDG-PET scan is a sensitive tool for staging patients with melanoma, the myocardium's reliance on fatty acids, carbohydrates, and ketone bodies for its energy needs results in variable physiologic FDG uptake.[5] Cardiac metastasis is thus most reliably diagnosed with multiple imaging modalities, including TTE and cardiac MRI.[6]

The presence of cardiac metastasis is generally a sign of advanced disease.[4] However, as presented in our case, immunotherapy can be an effective treatment option for these patients.

The current standard of care first-line treatment of metastatic BRAF wild-type cutaneous melanomas is with immunotherapy.[7,8] Before immunotherapy, outcomes of patients diagnosed with metastatic melanoma were poor, with an estimated median overall survival (OS) of roughly 8 months and a 5-year OS rate of approximately 10%.[9]

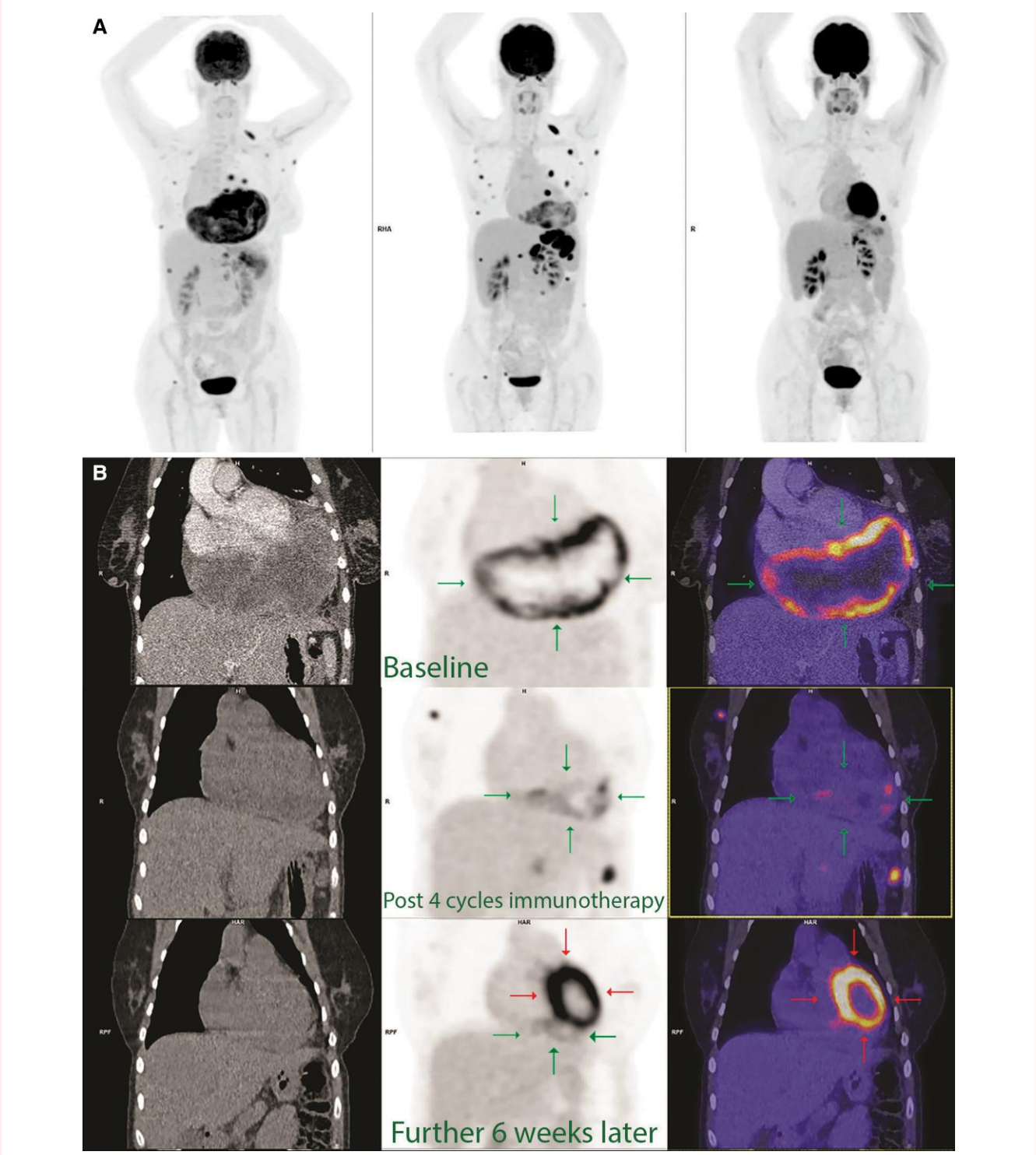


Figure 5 (*A*) Three-time-point whole-body positron emission tomography images at baseline, post-four cycles of induction immunotherapy and 6 weeks later (from left to right). (*B*) Three-time-point positron emission tomography–computed tomography images showing the large fluorodeoxyglucose cardiac mass (marked with green arrows) at baseline (top row), significantly improved following four cycles of induction immunotherapy (middle row), and almost completely resolved 6 weeks later (bottom row). Note the concentric normal physiologic left ventricular cardiac fluorodeoxyglucose uptake in the most recent scan (bottom row, marked with red arrows).

Outcomes have significantly improved since, perhaps best illustrated by the updated long-term outcomes from the Phase III CheckMate 067 trial.[10] In this study, patients with previously untreated advanced melanoma were randomly assigned to receive either a combination of ipilimumab and nivolumab, nivolumab alone, or ipilimumab alone.[11] Median OS for patients assigned combination ipilimumab and nivolumab

was 72.1 months vs. 36.9 months and 19.9 months in the nivolumab alone and ipilimumab alone arms, respectively.[10] This improvement was observed across clinically relevant subgroups, including PD-L1-negative tumours, tumours exhibiting a BRAF mutation, and patients with a baseline elevated LDH level.[11] Another key benefit of combination immunotherapy is that it offers patients with metastatic melanoma the potential to be treatment-free with durable clinical benefits seen even in patients who had subsequently discontinued treatment.[10]

The potential benefits need to be carefully weighed against the high rates of toxicity observed with combination immunotherapy.[11] In the CheckMate 067 trial, Grade 3 or 4 adverse events occurred in 59% of patients treated with combination immunotherapy vs. 21% and 28% in the nivolumab alone and ipilimumab alone arms, respectively.[11]

An important limitation of the CheckMate 067 trial was the exclusion of patients with untreated brain metastasis that would have included this case.[12] Two phase II trials addressed this: the ABC study and the CheckMate 204.[13,14] In these trials, intracranial responses in patients with asymptomatic and previously untreated brain metastasis were 46% and 57%, respectively, following treatment with combination ipilimumab and nivolumab with durable survival reported.[13,14] Combination immunotherapy is thus an option for patients with small, asymptomatic brain metastasis although they warrant careful monitoring for central nervous system disease progression necessitating local therapy as was required in our case.

With the evolving treatment landscape for advanced melanomas, considerations for surgery have become complex, highlighting the importance of a multidisciplinary team approach.[4] In highly selected patients with oligometastatic disease amenable to complete resection, surgical metastasectomy may produce durable benefits.[15] In this cohort of patients, relapse rates remain high, and consensus guidelines recommend adjuvant immunotherapy.[7]

Conclusion

Through our case report, we hope to highlight that immunotherapy can be an effective treatment even for large unresectable pericardial metastasis, and cardiac function can recover with a response to treatment.

Lead author biography

Ek Leone Oh is a medical oncology trainee based at Fiona Staley Hospital in Western Australia. He is currently undertaking a WA Research Cancer Fellowship.

Supplementary material

Supplementary material is available at *European Heart Journal – Case Reports* online.

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Conflict of interest: The authors declare that there is no conflict of interest.

Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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