A case report: metastasis of melanoma to the heart in an era of immunotherapy

Christian B. Poulsen 1,2*, Kathrine S. Weile 3,4, Henrik Schmidt 4, and Steen H. Poulsen 2

1Department of Cardiology, Regional Hospital West Jutland, Gl. Landevej 61, DK-7400 Herning, Denmark; 2Department of Cardiology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus, Denmark; 3Department of Medicine, Regional Hospital West Jutland, Gl. Landevej 61, DK-7400, Herning, Denmark; and 4Department of Oncology, Aarhus University Hospital, Palle Juul-Jensens Boulevard 99, DK-8200 Aarhus, Denmark

Received 10 April 2019; first decision 4 June 2019; accepted 25 September 2019; online publish-ahead-of-print 26 October 2019

Background
Cardiac metastasis of melanoma rarely causes heart failure symptoms and the recognition of cardiac involvement is in most cases first established post-mortem. Surgical removal might be considered in selected cases in patients with an inflow or outflow tract obstruction even though the survival remains poor. Frequently, the metastasis cannot be removed and therapeutic options include conventional chemotherapy or immunotherapy, which is currently recommended as first-line treatment. Since the introduction of immunotherapy survival in metastatic disease has significantly increased but data on patients treated for melanoma with cardiac involvement are scarce.

Case summary
A 65-year-old man presented with dyspnoea and fatigue. Computed tomography scan revealed tumour processes in the heart, which was confirmed on echocardiography. Biopsies taken from fluorodeoxyglucose positron emission tomography positive lymph nodes in the axilla and groin showed melanoma. Analyses did not reveal BRAF mutation and the PD-L1 expression in tumour cells was below 1%. Treatment with ipilimumab and nivolumab was initiated and cardiopulmonary symptoms subsided during the following months with significant reduction in cardiac metastasis on echocardiography. Unfortunately, the patient developed immune checkpoint inhibitor-induced colitis and could no longer continue on the therapy. Due to development of extra-cardiac and cerebral metastasis, he was referred to palliative care.

Discussion
This case demonstrates that timely treatment with immunotherapy could be a safe and effective option for melanoma with cardiac involvement. During treatment, the patient developed severe colitis, a known side effect to immunotherapy. Though this often can be managed with steroids it complicates further treatment.

Keywords
Case report • Melanoma • Cardiac metastasis • Echocardiography

Learning points
- Immunotherapy is effective in reducing cardiac metastasis of malignant melanoma without causing adverse cardiac events in the majority of patients.
- Therapy-induced colitis constitutes a significant clinical problem in this patient population.
- Melanoma patients with elevated troponin, N-terminal pro-B-type brain natriuretic peptide, or electrocardiogram changes should be referred for cardiac evaluation.

* Corresponding author. Tel: +4578450000, Email: chspou@rm.dk
Handling Editor: Georg Goliasch
Peer-reviewers: Joseph Moutiris, Hugo Rodriguez-Zanella, and Timothy C. Tan
Compliance Editor: Anastasia Vamvakidou
Supplementary Material Editor: Ross Thomson

© The Author(s) 2019. Published by Oxford University Press on behalf of the European Society of Cardiology.
This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0/), which permits unrestricted reuse, distribution, and reproduction in any medium, provided the original work is properly cited.
Introduction

Melanoma carries a dismal prognosis with an increasing incidence reaching 19 cases per 100,000 in Northern Europe and thus constitutes a burden to public health. Cardiac metastasis has been documented in 47.2% of patients with melanoma post-mortem but in the majority of cases it was clinically silent. When cardiac involvement is diagnosed ante-mortem, symptoms are often related to tumour location and varies from functional dyspnoea, chest pain to dizziness, or syncope. Since the introduction of immunotherapy in melanoma management, survival has improved significantly for metastatic disease however when cardiac involvement is present data are lacking in regard to prognosis and response to treatment.

Case presentation

A 65-year-old Caucasian male was referred from his general practitioner after complaining of fatigue and shortness of breath at moderate exertion for 3–5 weeks. He had no prior medical history and did not use any prescribed medication. A computed tomography (CT) scan of the chest and abdomen revealed multiple enlarged lymph nodes in the mediastinum and retroperitoneum. A large infiltrating tumour was found in the left ventricle along with a small pericardial effusion (Figure 1A) and sub-segmental pulmonary atelectasis. At physical examination, heart and lung auscultations were unremarkable and no signs of ascites or peripheral oedema were present. No cutaneous lesions were found though multiple hard subcutaneous masses were felt on palpation of the chest and abdomen. Saturation was 96% while breathing ambient air. Blood pressure was 123/85 mmHg and heart rate 100 b.p.m. The electrocardiogram

Timeline

| Time        | Event                                      | Findings                                                                 |
|-------------|--------------------------------------------|--------------------------------------------------------------------------|
| August 2018 | Fatigue and dyspnoea.                      |                                                                           |
| September 3 | Clinical evaluation by general practitioner.|                                                                           |
| September 27| Computed tomography (CT) scan of chest and abdomen. | Tumour infiltration in left ventricle and multiple enlarged lymph nodes in the mediastinum and retro peritoneum. |
| October 2   | Hospital consultation and echocardiography (Figure 1C). | Tumour in the right ventricle and ventricular septum.                      |
| October 8   | Fluorodeoxyglucose positron emission tomography scan (Figure 1D). | Multiple fluorodeoxyglucose positive masses in the heart, right lung, and lymph nodes in the groin. |
| October 9   | Biopsy from lymph nodes.                   |                                                                           |
| October 13  | Pathology shows malignant melanoma.        |                                                                           |
| October 18  | Cardiac evaluation and echocardiography (Figures 1E and 2A–C). Blurred vision, referred to cerebral magnetic resonance imaging (MRI). Commences prednisolone treatment. | Multiple cardiac metastases were found on contrast echocardiography. Cerebral MRI shows metastasis in left occipital and temporal lobe. |
| October 24  | Pathology shows no BRAF mutation or PD-L1 expression. |                                                                           |
| October 25  | Cardiac MRI (Figure 1F).                   | Extensive metastatic infiltration in the left ventricle.                  |
| November 1  | First treatment with ipilimumab 78 mg and nivolumab 235 mg. |                                                                           |
| November 23 | Second treatment with ipilimumab 78 mg and nivolumab 235 mg. |                                                                           |
| December 14 | Third treatment with ipilimumab 78 mg and nivolumab 235 mg. |                                                                           |
| December 17 | Cardiac evaluation with echocardiography (Figure 2D–F). | Regression in metastatic size.                                             |
| December 20 | Diarrhoea.                                 |                                                                           |
| January 7, 2019 | Persistent diarrhoea, commences infliximab. |                                                                           |
| January 29  | Routine cerebral MRI and CT scan of the chest and abdomen after commencing immunotherapy. Echocardiography (Figure 3B and C). | Progression of metastasis on cerebral MRI. Computed tomography scan reveals progression of extra-cardiac metastasis. Echocardiography shows persistent reduction in cardiac metastasis and improvement in global longitudinal strain score. |
| February 1  | Referred to palliative care.               |                                                                           |
(ECG) showed sinus rhythm with low voltage and T-wave inversion in the inferior leads suggestive of myocardial involvement (Figure 1B). Echocardiogram revealed masses in the right ventricle and interventricular septum (Figure 1C), with normal left ventricular ejection fraction >60% and preserved diastolic function. A positron emission tomography (PET) scan revealed multiple fluorodeoxyglucose (FDG) positive masses in the heart (Figure 1D), right lung, and lymph nodes in the thorax and groin. Consistent with the FDG-PET scan multiple cardiac metastases were found on contrast echocardiography (Figure 1E) and extensive myocardial infiltration was present on

Figure 1 (A) Computed tomography scan of the chest showing an infiltrating tumour (arrow) in the interventricular septum. IVS, interventricular septum; LV, left ventricle; RV, right ventricle. (B) Electrocardiogram with low voltage and inverted T waves in inferior leads (II, III, and aVF). (C) Echocardiogram showing metastasis in the interventricular septum and right ventricle (arrows). (D) Fluorodeoxyglucose positron emission tomography combined with computed tomography in the same region as shown in A in addition to the tumour located in the interventricular septum additional metastatic processes are visible in the myocardium of both right and left ventricles. (E) Contrast echocardiography showing multiple metastasis in the septum and left ventricle (arrows). (F) Cardiac magnetic resonance imaging showing extensive melanoma infiltration in left ventricle (T1 weighted sequence).
cardiac magnetic resonance imaging (MRI, Figure 1F). No involvement of the cardiac valves was found on echocardiography, cardiac MRI, or FDG-PET.

Biopsies taken from FDG positive lymph nodes showed malignant melanoma and subsequent analysis did not reveal BRAF mutation or PD-L1 expression. Shortly after, the patient developed blurred vision and a cerebral MRI revealed metastasis in the left occipital and temporal lobe. To manage symptoms, the patient commenced treatment with prednisolone 50 mg once daily and was subsequently reduced to 12.5 mg daily during the following weeks. Due to the patient’s metastatic disease with cerebral involvement, he was referred for combination therapy with ipilimumab 78 mg (anti-CTLA 4 antibody) and nivolumab 235 mg (anti-PD-1 antibody) every third week while on steroid treatment. Laboratory studies showed elevated N-terminal pro-B-type brain natriuretic peptide (NT-pro-BNP) 1391 ng/L (<300 ng/L) and troponin T, 21 ng/L (<14 ng/L). At the time of second treatment, NT-pro-BNP and troponin T increased to 3774 ng/L and 62 ng/L, respectively, suggestive of myocardial injury secondary to immunotherapy. After completing the third treatment, the patient felt a complete relief of his initial symptoms of dyspnoea and fatigue. Clinical evaluation showed reduction in subcutaneous metastasis and the ECG revealed sinus rhythm with normalisation of T waves in the inferior leads. Subsequent echocardiography confirmed reduction in the size of cardiac metastasis (Figure 2D and E) however GLS score did not improve (-12.9%) on average (Figure 2F).

Laboratory studies showed reduced NT-pro-BNP 1074 ng/L and TnT 20 ng/L. Following cardiac evaluation, the patient developed severe colitis for which immunotherapy was discontinued and his gastrointestinal symptoms managed by one treatment of TNF-alpha antibody (infliximab 5 mg/kg) and methylprednisolone 80 mg daily for 1 week. The patient subsequently resumed oral steroid treatment initially with prednisolone 75 mg once daily and was gradually reduced during the following weeks to 25 mg daily.

A routine MRI scan performed 3 months after treatment initiation revealed progression of cerebral metastasis and CT scan of the thorax and abdomen showed increase in extra-cardiac metastasis, a small peripheral pulmonary embolus, and no pleural effusions. Clinical evaluation revealed unremarkable ECG (Figure 3A), persistent reduction in cardiac metastasis on echocardiography (Figure 3B) and a notable improvement in GLS score to -14.9% on average with normalization of contraction pattern and Troponin I < 10 ng/L. No signs of increased pulmonary pressure was observed. Pulmonary embolism was treated with weight-adjusted low-molecular heparin daily. Due to deteriorating cognitive function and progression of extra-cardiac metastasis prednisolone dose was increased to 75 mg daily and the patient was referred to palliative care.

Discussion

We present a case of symptomatic cardiac melanoma, treated with immune checkpoint inhibitors resulting in regression of cardiopulmonary symptoms and reduction in cardiac metastatic size, which persisted 6 weeks after discontinuation of therapy. To our
Figure 3 (A) Electrocardiogram obtained 12 weeks after treatment initiation with normalization of T waves in inferior leads (II, III, and aVF). (B) Echocardiogram obtained 12 weeks after treatment initiation showing persistent reduction in cardiac metastatic size (arrows) with improvement in global longitudinal strain and normalization of contraction pattern (C).
knowledge, this is the first report of cardiac melanoma treated with both nivolumab and nivolumab.

A decade ago metastatic melanoma had a 5-year survival rate of 5–10% on standard chemotherapies but with the introduction of immunotherapies in 2011 survival rates have been increasing.\(^{10,11}\) Nivolumab has significantly prolonged overall survival compared with conventional chemotherapy (dacarbazine)\(^ {12}\) and in CheckMate 067 treatment with ipilimumab and nivolumab prolonged survival compared with ipilimumab after 4 years of follow-up.\(^ {13}\)

When cardiac melanoma is present, the most common location is in relation to the right-sided heart chambers.\(^ {14}\) Though melanoma in the heart has been observed in up to 47.2% of patients post-mortem, finding patients presenting with symptoms primarily relating to the cardiovascular system is rare.\(^ {2,3}\) Patients without cardiac symptoms should therefore be offered a screening of cardiac involvement by ECG, troponins, and NT-pro-BNP and in cases of abnormalities a two- and three-dimensional echocardiography should be performed to identify conditions such as; outflow tract obstruction, pericardial effusion, or signs of pulmonary embolism. In symptomatic cases with significant obstructive tumour masses cardiac surgery might be an option, but even with early surgical intervention prognosis remain poor mainly due to diffuse myocardial infiltration and metastasis in other organ systems.\(^ {4}\) Though the patient had extra-cardiac metastasis that progressed during immunotherapy, this case demonstrates that treatment with ipilimumab and nivolumab vary rarely affects cardiac function and provides clinical benefits in patients with cardiac melanoma.

With the increased use of immune checkpoint inhibitors, toxicity is increasingly recognized as a clinical problem. For patients treated with ipilimumab and nivolumab, the most common symptoms are gastrointestinal. Particular diarrhoea which occurs in up to 30% of patients in clinical trials treated with ipilimumab.\(^ {15}\) The patient discussed did develop immune checkpoint inhibitor-induced colitis and his symptoms were managed by administration of prednisolone and TNF-alpha antibody (infliximab). However, due to the severity of the colitis, the patient was not able to continue immunotherapy. A rare but serious toxic effect is immune-mediated myocarditis, which has been reported in 0.27% of patients treated with ipilimumab and nivolumab.\(^ {16}\) This diagnosis should be considered if patients present with clinical deterioration in the weeks following treatment initiation.

Brain metastases are common in patients with melanoma and are found in more than 75% of cases at the time of death.\(^ {17}\) Historically prognosis has been poor with a median overall survival of 2–5 months and only 5% surviving in the long-term (>5 years). Due to its poor prognosis randomized phase III trials are warranted but data from a randomized phase II study suggest that this population might benefit from combination therapy as well.\(^ {18,19}\) In the current case, the patient initially reported regression of cerebral melanoma symptoms but had increased cognitive problems and progression of cerebral metastasis on magnetic resonance while on combination therapy.

**Conclusion**

Despite cerebral progression of melanoma, this case demonstrates clinical benefits of treating cardiac melanoma with ipilimumab and nivolumab causing regression of cardiopulmonary symptoms and metastatic size.

**Lead author biography**

Christian B. Poulsen is a senior registrar in cardiology at the Regional Hospital West Jutland in Herning, Denmark. He has previously performed experimental studies of atherosclerosis in porcine models as part of his PhD.

**Supplementary material**

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

**Slide sets:** A fully edited slide set detailing this case and suitable for local presentation is available online as Supplementary data.

**Consent:** The author/s confirm that written consent for submission and publication of this case report including image(s) and associated text has been obtained from the patient in line with COPE guidance.

**Conflict of interest:** none declared.

**References**

1. Nikolou V, Stratigos AJ. Emerging trends in the epidemiology of melanoma. Br J Dermatol 2014; **170**:11–19.
2. Patel JK, Didolkar MS, Pickren JW, Moore RH. Metastatic pattern of malignant melanoma. A study of 216 autopsy cases. Am J Surg 1978; **135**:807–810.
3. Maleszewski JJ, Bois MC, Bois JP, Young PM, Stulak JM, Klarich KW. Neoplasia and the heart: pathological review of effects with clinical and radiological correlation. Am Coll Cardiol 2018; **72**:202–227.
4. Onan B, Onan IS, Polat B. Surgical resection of solitary metastasis of malignant melanoma to the right atrium. Tex Heart Inst J 2010; **37**:598–601.
5. Goldberg AD, Blankstein R, Padera RF. Tumors metastatic to the heart. Circulation 2013; **128**:1790–1794.
6. Hanna TP, Nguyen P, Batz T, Booth CM, Eisenhauer E. A population-based study of survival impact of new targeted and immune-based therapies for metastatic or unresectable melanoma. Clin Oncol (R Coll Radiol) 2018; **30**:609–617.
7. Cates CU, Virmani R, Vaughn WK, Robertson RM. Electrocardiographic markers of cardiac metastasis. Am Heart J 1986; **112**:1297–1303.
8. Peliter MS, Amaria RN. Combined targeted therapy and immunotherapy in melanoma: a review of the impact on the tumor microenvironment and outcomes of early clinical trials. Ther Adv Med Oncol 2017; **11**:1758835917830826.
9. Collier P, Phelan D, Klein A A text in context: myocardial strain measured by speckle-tracking echocardiography. J Am Coll Cardiol 2017; **69**:1043–1056.
10. Franklin C, Livingstone E, Roessch A, Schilling B, Schadendorf D. Immunotherapy in melanoma: recent advances and future directions. Eur J Surg Oncol 2017; **43**:604–611.
11. Uprety D, Bista A, Chennamadmavuni A, Irioula A, Jafri SIM, Smith A, Arjyal L. Survival trends among patients with metastatic melanoma in the pretargeted and the post-targeted era: a US population-based study. Melanoma Res 2018; **28**:36–60.
12. Garbe C, Peris K, Hauschild A, Saag P, Middleton M, Bachtel L, Grab JJ, Malvehy J, Newton-Booth J, Stratigos AJ, Pehamberger H, Eggermont AM. Diagnosis and treatment of melanoma. European consensus-based interdisciplinary guideline—update 2016. Eur J Cancer 2016; **63**:201–217.
13. Hodi FS, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rustowksi P, Cowey CL, Lao CD, Schadendorf D, Wagstaff J, Dummer R, Ferrucci PF, Smylie M, Hall A, Hogg D, Marquez-Rodas I, Jiang J, Rizzo J, Larkin J, Wolchok JD. Nivolumab plus ipilimumab or nivolumab alone versus ipilimumab alone in advanced melanoma (CheckMate 067): 4-year outcomes of a multicentre, randomised, phase 3 trial. Lancet Oncol 2018;19:1480–1492.

14. Parissis H, Al-Alao BS, Young VK. Case report and literature review: surgical treatment of a right atrial metastatic melanoma from a previously resected ‘advanced’ primary site with regional lymph nodes involvement. Gen Thorac Cardiovasc Surg 2012;60:655–660.

15. Prieux-Klotz C, Dior M, Damotte D, Dreianc J, Brieau B, Brezault C, Abitbol V, Chaussade S, Coriat R. Immune checkpoint inhibitor-induced colitis: diagnosis and management. Targ Oncol 2017;12:301–308.

16. Johnson DB, Balko JM, Compton ML, Chalkias S, Gorham J, Xu Y, Hicks M, Puzanov I, Alexander MR, Bloomer TL, Becker JR, Slosky DA, Phillips EJ, Pilkinton MA, Craig-Owens L, Kola N, Plautz G, Reshef DS, Deutsch JS, Deering RP, Olenchock BA, Lichtman AH, Roden DM, Seidman CE, Koralnik JJ, Seidman JG, Hoffman RD, Taube JM, Diaz LA, Anders RA, Sosman JA, Moslehi JJ. Fulminant myocarditis with combination immune checkpoint blockade. N Engl J Med 2016;375:1749–1755.

17. Sloan AE, Nock CJ, Einstein DB. Diagnosis and treatment of melanoma brain metastasis: a literature review. Cancer Control 2009;16:248–255.

18. Tawbi HA, Forysth PA, Aligaz A, Hamid O, Hodi FS, Moschos SJ, Khushalani NI, Lewis K, Lao CD, Postow MA, Atkins MB, Ernstoff MS, Reardon DA, Puzanov I, Kudchadkar RR, Thomas RP, Tarhini A, Pavlick AC, Jiang J, Avila A, Demelo S, Margolin K. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med 2018;379:722–730.

19. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, Wilmott JS, Edwards J, Gonzalez M, Scolyer RA, McArthur GA. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. Lancet Oncal 2018;19:672–681.