ABSTRACT

Introduction: Nivolumab is an immune checkpoint inhibitor (ICI) in a class of immunomodulators used to treat various cancers, including melanoma. Here we present ICI-related cardiomyopathy leading to patient death.

Case Report: An 88-year-old female receiving therapy for metastatic melanoma with ICI-Nivolumab presented with acute hypoxic respiratory failure secondary to new onset acute combined systolic and diastolic heart failure. She had no known cardiac history and was on minimal medication prior to presentation. After extensive workup, including pleural fluid analysis, a cardiac magnetic resonance, and left heart catheterization, no other cause could be attributed to her cardiac dysfunction other than adverse medication event due to immunomodulation therapy with Nivolumab.

Discussion: Cardiomyopathy is a rare but potentially life-threatening complication of ICI therapy and should be considered when discussing treatment modalities with patients, especially in high-risk populations.

KEYWORDS  nivolumab, immune checkpoint inhibitor, cardiomyopathy, melanoma

Introduction

The mainstay of the treatment of melanoma relies heavily on early staging, surgical intervention, and intrallesional therapy. With the advent of immunomodulation therapy, patients with evidence of metastatic disease or those at risk have shown benefits with adjuvant therapy. Nivolumab is one such therapy in a class of immunomodulators known as an immune checkpoint inhibitors (ICI). It inhibits the programmed cell death receptor 1 (PD-1) on T-cells, so PD-1 cannot bind to ligands PD-L1 and PD-2 on tumour cells. This mechanism stimulates memory response to those tumour antigens. Nivolumab alone or in conjunction with ipilimumab has shown to be more beneficial for response rate, stable disease rate, and progression-free survival than other metastatic melanoma agents. It was approved by the FDA in 2015. Despite anti-PD-1 having less risk of adverse events than chemotherapy and ipilimumab, the high-risk adverse events (AE) rate is frequent in almost half of patients. Furthermore, ICI drugs have been related to life-threatening cardiotoxicities, such as ventricular arrhythmia, pulmonary embolism, heart failure and cardiac arrest. Potential mechanism consists of CD4+/CD8+ T-cells infiltration in cardiomyocytes, producing pro-apoptotic enzymes. It even has been evidenced in the in-vitro model. Invasion is attributed to “shared antigen” between tumour cells and cardiomyocytes. However, there is a debate whether some rare AE, like dilated cardiomyopathy, has an inflammatory or non-inflammatory mechanism.

We present a Nivolumab-related dilated cardiomyopathy that led to combined systolic and diastolic heart failure in an older woman with metastatic melanoma.

Case Report

An 88-year-old caucasian female with a history of diverticulosis with a recent bout of diverticulitis on augmentin, pre-diabetes, hypertension, and metastatic melanoma is currently receiving treatment with Nivolumab and Talimogene laherparevec (intrallesional), presented to the emergency room with a chief com-
plaint of progressively worsening dyspnea for five days. She also complained of orthopnea, dry cough, and pleuritic chest pain that worsened when lying flat. She denied paroxysmal nocturnal dyspnea, fever, or chills. She did not complain of lower extremity swelling. She denied any gastrointestinal or genitourinary complaints. She was previously active for her age and was not using any oxygen at home. Physical exam on presentation was notable for evidence of jugular venous distention. It decreased breath sounds at bilateral lung bases with fine crackles throughout mid lobes. A cardiovascular exam noted an S3 with a regular rate and rhythm. The abdomen was soft, non-tender and non-distended. No lower extremity edema was noted. She had a cardiac echocardiogram performed in 2015, showing a left ventricular ejection fraction (LVEF) of 50-55%, with no diastolic dysfunction or significant valvar abnormalities. Her advanced melanoma was negative for metastasis on a PET scan in late 2019. She had developed the in-transit disease after local excision of an initial skin lesion with multiple subcutaneous lesions near the excision site. These were considered when planned treatment options were presented and discussed. Nivolumab 240 mg intravenously every two weeks and Talimogene laherparevec (intralesional) injections every two weeks had been started four months prior to presentation. Family and social history were non-contributory. Given the history and the presentation, the patient was diagnosed with acute hypoxic respiratory failure secondary to acute heart failure.

Initial laboratory values included a brain natriuretic peptide (BNP) level of 530 pg/ml and high sensitivity troponin level of 130 ng/L. The basic metabolic panel and complete blood count were within normal limits.

The electrocardiogram showed normal sinus rhythm without evidence of arrhythmia or acute ST- changes. Initial chest x-ray showed evidence of moderate left-sided with mild right-sided pleural effusions. A computed tomography angiogram of the chest confirmed evidence of bilateral pleural effusions without evidence of pulmonary embolism (Figure 1).

The patient was treated empirically for suspected heart failure with intravenous diuretic therapy and had a left thoracentesis performed by interventional radiology. The patient responded quickly. All symptoms improved markedly, and she was able to breathe comfortably on room air. An echocardiogram showed an LVEF of 20-25% with severe global hypokinesis. Repeat chest x-ray indicated that most of the pleural effusion had resolved, with only minimal right-sided pleural effusion remaining. Pleural fluid analysis was consistent with transudate. There was no evidence of malignancy on cytology or infection on gram stain.

As for the cause of the new onset of combined systolic and diastolic heart failure, the oncology and medical team were concerned about possible myocarditis related to the recent Nivolumab therapy. Cardiac magnetic resonance imaging indicated an LVEF of 23% but no evidence of myocarditis or any infiltrative process (Figure 2, Figure 3). Left heart catheterization was then performed and showed LVEF of 25%, severe global hypokinesia, left ventricular end-diastolic pressure of 7 mmHg, and no evidence of coronary artery disease, which did not explain the degree of left ventricular dysfunction.

The patient was started on guideline-directed medical therapy with metoprolol, in addition to the medication of spironolactone and losartan. Formal recommendation from cardiology and oncology was against continued Nivolumab, given cardiomyopathy could not be explained any other way. Given her left ventricular function, she was planning for an implantable cardiac defibrillator. The plan was to continue guideline-directed medical therapy, follow-up in three months, and the discontinuation of immunotherapy. Unfortunately, the patient died unexpectedly 32 days after discharge. No repeated echocardiogram was performed prior to death. No autopsy was performed.

**Discussion**

Cardiomyopathy related to ICI is an infrequent AE, and the mechanism is still unclear compared to other AE. “The most likely explanation is the ‘shared antigen’ between the tumour and cardiac muscle, with muscle-specific antigens (desmin and troponin) detected in the tumour.”

This mechanism is likely clinically significant since prior case reports had fatal results due to steroid-refractory myocarditis and myocardial necrosis.11,12

Cardiomyopathy is a rare complication of drugs acting on the PD-1/PD-L1 axis. However, a longer follow-up may allow the identification of more cases since cardiomyopathy often results from long-term therapy.20 For instance, a prior cohort of patients with non-small-cell lung cancer undergoing PD-1/PD-L1 drugs showed that cardiomyopathy prevalence at one month was 0.22%. Still, it increased to 1.02% at nine months.18 In
a trial of patients with advanced melanoma, cardiomyopathy was presented 100 days after the last dose of Nivolumab plus Ipilimumab. The extensive work-up in our case presentation was unable to produce a clear culprit for the cause of her cardiomyopathy.

We concluded that the only clear explanation for her presentation is the immunotherapy with Nivolumab. The laboratory findings in our patient suggested injury of cardiomyocytes (elevated troponins and BNP); therefore, the most plausible mechanism is via hyper-infiltration of T-cells that damages the myocardial tissue.

Conclusion

Our clinical case highlights the importance of long-term follow-up of cancer patients consuming ICI since rare cardiac AE presents after several months.

Cardiomyopathy is life-threatening in this population since it leads to acute heart failure and death. Evaluating the risks and benefits with patients should include the potential for cardiotoxicity, especially in the elderly population. We hope to add to the understanding and the growing literature on the risks and potential AEs of ICI therapy so that physicians and patients can stay adequately informed when choosing the proper therapy.

Abbreviations

ICI : immune checkpoint inhibitor
PD-1 : programmed cell death receptor 1
PD-L1 : Programmed cell death ligand 1
PD-L2 : Programmed cell death ligand 2
FDA : Food and Drug Agency
AE : Adverse Event
LVEF : left ventricular ejection fraction
PET : Positron emission tomography
BNP : brain natriuretic peptide
ng/L : nanograms per litre
mmHg : millimetre per mercury

Acknowledgments

We would like to acknowledge our program director Dr Scott Friedstrom MD for his support.

Ethical Considerations

Written informed consent was obtained prior to death. Institutional Review Board approval not needed as the manuscript is a case report. All information was obtained ethically and with patient consent.

Disclaimers/Conflict of Interest/Funding

This research project was self-funded. This research did not receive any specific grant from public, commercial, or not-for-profit funding agencies. The authors declare no conflicts of interest.

Author Contributions

Timothy McCann MD contributed to the conception and design of the work, acquisition of data, analysis of data and interpretation of data. Also significantly contributed to drafting and revising the work critically for important intellectual content.

Contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Stephen P. Beerman MD contributed to the conception and design of the work and to revising the work critically for important intellectual content. Contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Hatem Elabd MD contributed to the conception and design of the work and contributed to revising the work critically for important intellectual content. Contributed to final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Contributions

All authors have approved the final article.

Guarantor of Submission

The corresponding author is the guarantor of submission.

References

1. Guo L, Zhang H, Chen B. Nivolumab as Programmed Death-1 (PD-1) Inhibitor for Targeted Immunotherapy in Tumor. J Cancer. 2017;8(3):410-6.
2. Menshawy A, Eltonob AA, Barkat SA, Ghanem A, Mniesy MM, Mohamed I, et al. Nivolumab monotherapy or in combination with ipilimumab for metastatic melanoma: systematic review and meta-analysis of randomized-controlled trials. Melanoma Res. 2018;28(5):371-9.

3. Hao C, Tian J, Liu H, Li F, Niu H, Zhu B. Efficacy and safety of anti-PD-1 and anti-PD-1 combined with anti-CTLA-4 immunotherapy to advanced melanoma. Medicine (Baltimore). 2017;96(26).

4. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined Nivolumab and Ipilimumab or Monotherapy in Untreated Melanoma. New England Journal of Medicine. 2015;373(1):23-

5. Almutairi AR, McBride A, Slack M, Erstad BL, Abraham I. Potential Immune-Related Adverse Events Associated With Monotherapy and Combination Therapy of Ipilimumab, Nivolumab, and Pembrolizumab for Advanced Melanoma: A Systematic Review and Meta-Analysis. Front Oncol. 2020;10.

6. Escudier Marion, Cautela Jennifer, Malissen Nausicaa, Anced y Yann, Ora bona Morgane, Pinto Johan, et al. Clinical Features, Management, and Outcomes of Immune Checkpoint Inhibitor-Related Cardiotoxicity. Circulation. 2017;136(21):2085-7.

7. Zhou Y-W, Zhu Y-J, Wang M-N, Xie Y, Chen C-Y, Zhang T, et al. Immune Checkpoint Inhibitor-Associated Cardiotoxicity: Current Understanding on Its Mechanism, Diagnosis and Management. Frontiers in Pharmacology. 2019;10.

8. Tay WT, Fang Y-H, Beh ST, Liu Y-W, Hsu L-W, Yen C-J, et al. Programmed Cell Death-1: Programmed Cell Death-Ligand 1 Interaction Protects Human Cardiomyocytes Against T-Cell Mediated Inflammation and Apoptosis Response In Vitro. Int J Mol Sci. 2020;21(7).

9. Varricchi Gilda, Galdiero Maria Rosaria, Tocchetti Carlo G. Cardiac Toxicity of Immune Checkpoint Inhibitors. Circulation. 2017;136(21):1989-92.

10. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. The Lancet Oncology. 2018;19(9):e447-58.

11. Saibil SD, Bonilla L, Majeed H, Sotov V, Hogg D, Chappell MA, et al. Fatal myocarditis and rhabdomyositis in a patient with stage IV melanoma treated with combined ipilimumab and nivolumab. Curr Oncol. 2019;26(3):e418-21.

12. Sakai T, Yahagi K, Hoshino T, Yokota T, Tanabe K, Mori M, et al. Nivolumab-induced myocardial necrosis in a patient with lung cancer: A case report. Respir Med Case Rep. 2019;27.

13. Antonia SJ, López-Martin JA, Bendell J, Ott PA, Taylor M, Eder JP, et al. Nivolumab alone and nivolumab plus ipilimumab in recurrent small-cell lung cancer (CheckMate 032): a multicentre, open-label, phase 1/2 trial. The Lancet Oncology. 2016;17(7):883-95.

14. Zimmer L, Goldinger SM, Hofmann L, Loquai C, Ugere l S, Thomas I, et al. Neurological, respiratory, musculoskeletal, cardiac and ocular side-effects of anti-PD-1 therapy. Eur J Cancer. 2016;60:210-25.

15. Antonia SJ, Villegas A, Daniel D, Vicente D, Murakami S, Hui R, et al. Durvalumab after Chemoradiotherapy in Stage III Non-Small-Cell Lung Cancer. N Engl J Med. 2017;377:1919- 1929.

16. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob J-J, Rutkowski P, Lao CD, et al. Five-Year Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. N Engl J Med. 2019;381(16):1535-4.

17. Loi S, Giobbie-Hurder A, Gombos A, Bachelot T, Hui R, Curigliano G, et al. Pembrolizumab plus trastuzumab in trastuzumab-resistant, advanced, HER2-positive breast cancer (PANACEA): a single-arm, multicentre, phase 1b-2 trial. Lancet Oncol. 2019;20(3):371- 82.

18. Cathcart-Rake EJ, Sangaralingham LR, Henk HJ, Shah ND, Riaz IB, Mansfield AS. A Population-based Study of Immunotherapy-related Toxici ties in Lung Cancer. Clinical Lung Cancer. 2020;21(5):421-

19. Waheed N, Fradley MG, DeRemer DL, Mahmoud A, Shah CP, Langae t NY, et al. Newly diagnosed cardiovascular disease in patients treated with immune checkpoint inhibitors: a retrospective analysis of patients at an academic tertiary care center. Cardiooncology. 2021;7(1):10.

20. Sisakian H. Cardiomyopathies: Evolution of pathogenesis concepts and potential for new therapies. World J Cardiol. 2014;6(6):478-94.