JACC: CASE REPORTS VOL. 1, NO. 1, 2019

EDITORIAL COMMENT

The Tale of a Double-Edged Sword

Protecting the Heart from Metastatic Melanoma Tumor and its Treatment with Pembrolizumab*

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Cardio-oncology is a field of medicine emerging at the intersection of cardiology and oncology. As the term implies, the field encompasses preventing (as applicable), monitoring, detecting, and managing primary and secondary cardiac tumors, as well as cardiotoxic effects of cancer therapy, in addition to diseases affecting the heart, such as amyloidosis, that may be treated with cytotoxic therapies. In the effort to prevent cardiotoxicity resulting from cancer pharmacotherapy, immunotherapy, or radiation, cardio-oncologists assess pre-existing cardiac risk factors or comorbidities in individuals who become survivors at the moment of receiving a cancer diagnosis (1). Measures are then put in place to manage cardiac disease, prevent barriers to effective cancer therapies, and reduce further cardiac damage or reverse any worsening cardiotoxic side effects of cancer therapies.

In cardio-oncology, primary lung cancers (36% to 39% of cases), breast cancers (10% to 12% of cases), and lymphomas (10% to 21% of cases) most frequently metastasize to the heart, attributed partly to their proximal location (2-4). These cancers can extend locally into the heart by direct or lymphatic dissemination and will often result in pericardial and epicardial involvement. However, other tumors such as melanoma have a tendency to metastasize to the heart by a hematogenous route, typically causing myocardial and endocardial invasion early in the disease course and contributing to the poor prognosis of patients with advanced stage melanoma. Other metastatic tumors may enter the heart by means of local continuous extension into the inferior or superior vena cava, where the first port of entry into the heart is the right atrium. Furthermore, there are many clinical presentations of cardiac metastases. Most commonly, metastases can be clinically silent, but they can also present with nonspecific signs or symptoms difficult to differentiate from other cardiopulmonary diseases, such as dyspnea, episodes of arrhythmia, and chest pain, or with life-threatening manifestations such as cardiac tamponade, lethal arrhythmia, cardiac rupture, or sudden death (3-6).

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In this issue of *JACC: Case Reports*, Larsen et al. (7) present an interesting case of a solitary metastatic tumor to the pericardial space (with apparent pericarditis as well as infiltration of the epicardium and resultant impairment of left ventricular function), as the initial presentation of an advanced stage melanoma. This case highlights the possibility of cardiac metastasis without initially overt cardiac symptoms (such as heart failure) and serves as a reminder that cardiac involvement can be occult or present with nonspecific systemic or new, unexplained cardiorespiratory symptoms.

This case also exemplifies the remarkable response of some individuals with advanced melanoma to treatment with pembrolizumab. Pembrolizumab is a humanized antibody to the programmed cell death-1 (PD-1) protein, which helps mediate the body's immune response to cancer cells. Such cancer immunotherapy has revolutionized modern oncology care, providing significant improvement in the prognosis of a wide spectrum of solid and hematological malignancies. Immune checkpoint inhibitors (ICIs) are the main therapeutic class at the forefront of

*Editorials published in *JACC: Case Reports* reflect the views of the authors and do not necessarily represent the views of *JACC: Case Reports* or the American College of Cardiology.

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ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2019.05.017

cancer immunotherapy. The first-generation class of ICIs is targeted to cytotoxic T-lymphocyte-associated antigen 4 (CTLA-4) and appears to be more cardiotoxic than the second- generation class of ICIs targeted to PD-1 or programmed death-ligand 1 (PD-L1) when used alone. When used in combination, the risk of cardiotoxicity is higher. Since March 2011, many ICIs have been approved by the U.S. Food and Drug Administration for the treatment of multiple cancers, including pembrolizumab, nivolumab, and cemiplimab (PD-1 inhibitors); atezolizumab, avelumab, durvalumab (PD-L1 inhibitors); and ipilimumab (CTLA-4 inhibitor) (8–9). These novel therapies have been introduced into the treatment of numerous cancers and have shown impressive survival benefits, especially in the care of patients with advanced melanoma. Although generally well tolerated, ICI therapies have been associated with immunity-related adverse events (irAEs) due to aberrant activity of autoreactive T cells. These adverse events are typically transient but can be severe. The most common cardiotoxicity is myocarditis, which can be fatal and may present with tachyarrhythmia, other conduction abnormalities, acute heart failure, or cardiac arrest. This indicates a crucial need for increased awareness, close monitoring, and rapid identification of irAEs, to prompt critical initiation of immunosuppression based on the severity of the irAEs (9–12).

It is important to acknowledge both the remarkable benefit and the potential risk inherent in the use of ICIs, which can present clinical challenges. It is therefore prudent to care for cancer survivors treated with ICIs in multidisciplinary teams of hematologists and oncologists, cardiologists, cardiac rehabilitation professionals, primary care providers, and others in the burgeoning field of (preventive) cardio-oncology in both clinical practice and clinical trials, to protect survivors' hearts, enhance their quality of life, and manage any cardiotoxicity that ensues.

The *JACC* journals, with the inauguration of *JACC: Case Reports* for clinical cases and *JACC: CardioOncology* for a variety of papers in the field, give a new perspective in the development of cardio-oncology as an emerging subspecialty. The future is bright for multidisciplinary collaborations, and discussion of cases such as the one published by Larsen et al. (7) helps advance the depth of our understanding in cardio-oncology.

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KEY WORDS cardiac metastases, cardio-oncology, cardiovascular imaging, immune checkpoint inhibitors