JACC: CARDIOONCOLOGY VOL. 1, NO. 2, 2019

EDITORIAL COMMENT

Cancer and Peripartum Cardiomyopathy

A Diabolic Couple*

Jean-Luc Balligand, MD, PhD

Peripartum cardiomyopathy (PPCM), with decreased ejection fraction (<45%) in the absence of other causes for heart failure, affects women in the last month of pregnancy or in the first months after delivery (1). Significant, albeit widely variable, mortality rates (from 2% in Germany to 12.6% in a small series from South Africa) have been reported (2). Although some predisposing factors have been identified, the pathogenic mechanisms of the disease are incompletely understood. Among risk factors, several reports have highlighted the exposure to anticancer, potentially cardiotoxic treatments before pregnancy (3), even in the absence of clinical cardiac dysfunction during or after cancer treatment. Conversely, heart failure may also favor cancer development (4), suggesting a reciprocal influence between cancer and PPCM.

SEE PAGE 196

In this issue of *JACC: CardioOncology*, Pfeffer et al. (5) offer some interesting insights on this relationship. They first compared the prevalence of cancer in a combined German-Swedish cohort of PPCM (236 patients in total, with a median follow-up of 33 months) versus the 10-year prevalence in age-matched women (age 0 to 49 years) from a German cancer registry. Strikingly, they found that the risk of cancer was 16-fold higher in the overall PPCM cohort. For those women who developed cancer after PPCM, even adjusting for the slight increase in breast cancer risk after late pregnancy (more often represented in PPCM cohorts), the risk was still 8-fold higher. Does PPCM induce cancer or does the history of cancer predispose to PPCM?

Looking then at the subgroup of patients with PPCM who had cancer before pregnancy (5), the authors noted that many had received chemotherapy or radiotherapy in childhood or adolescence. All had normal cardiac function before the occurrence of PPCM, but among those who recovered, patients with cancer displayed less complete recovery of left ventricular function after PPCM. This finding suggested that pregnancy may have strained their hearts and resulted in late toxicity, or that these patients may have more fragile hearts prone to both drug-induced cardiotoxicity and PPCM. To substantiate this theory, the team looked at exome-sequencing data available from a limited (n = 14) number of these patients. They indeed found that 43% of patients with PPCM and cancer had gene variants likely pathogenic (LP) or pathogenic (P) for dilated or hypertrophic cardiomyopathy (DCM/HCM) or for cancer predisposition syndrome (CPS), all related to the deoxyribonucleic acid damage response (DDR). These variants may explain the propensity to develop PPCM when pregnancy-associated cardiac stress is superimposed on cardiac damage accumulated after inefficient or partial repair of previous drug-induced toxicity.

Six cases were diagnosed with cancer at or after the occurrence of PPCM in the absence of anticancer cardiotoxic treatment; of these, 2 patients had prolactinoma, a condition with high, dysregulated production of the lactation hormone prolactin (5). This outcome is noteworthy, given the well-established pathogenic role of the 16-kDa prolactin fragment in inducing microvascular endothelial damage and ischemic cardiomyopathy (6). In the setting of PPCM, the prevailing oxidant stress during pregnancy is believed to activate the cleavage of the parent hormone to form its toxic fragment. Current guidelines

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

From the Pole of Pharmacology and Therapeutics (FATH), Institute for Clinical and Experimental Research (IREC), UCLouvain and Cliniques Universitaires Saint-Luc, Brussels, Belgium. Dr. Balligand has reported that he has no relationships relevant to the contents of this paper to disclose.

ISSN 2666-0873 https://doi.org/10.1016/j.jaccao.2019.10.005

propose (Class IIb recommendation) treating specific cases of PPCM by adding the dopaminergic agonist bromocriptine, in addition to standard care, to stop the production of prolactin (7), as was done in three-quarters of all the PPCM patients reported by Pfeffer et al. (5). Unfortunately, this treatment was not done in 1 of the patients with prolactinoma, the only one to require heart transplantation.

Would the variants for DCM/HCM expose pregnant women to PPCM, even in the absence of cancer history and treatment? The same LP/P variants (e.g., for *MYH7*, coding Myosin-Heavy Chain 7, or *TTN*, coding Titin) were indeed found, but here the small numbers (n = 6) preclude any definitive conclusions (5). Also, DDR variants were not found in PPCM patients without cancer, but again the numbers are too small to conclude. This may still be an interesting lead because variants in *ATM* (coding Ataxia Telangiectasia Mutated serine/threonine kinase, a master controller of cell cycle checkpoint and deoxyribonucleic acid damage response) and *BRCA1* (coding Breast Cancer 1, implicated in genomic stability and in inherited forms of breast and ovarian cancers) may promote heart failure, including from anthracycline cardiotoxicity (8), through an impaired stress response (9). For PPCM patients with a cancer history, the observation of LP/P or variants of unknown significance for CPS/DDR genes in one-half of them is intriguing and novel, and it deserves confirmatory longitudinal studies in childhood/adolescent cancer survivors to verify if they predispose to PPCM with or without cancer recurrence.

This brings the second proposition; that is, PPCM may promote cancer development. Preclinical data suggest that failing hearts may promote malignant transformation of pre-cancerous tumors (4). This action is believed to involve the systemic production of factors secreted by the failing heart that promote the growth of cancer cells. Elevated cardiac and inflammatory biomarkers in a large population study also predicted new-onset cancer independent of age, smoking status, and body mass index, suggesting that heart failure is associated with a higher risk of incident cancer (4). In the context of the present study (5), it is potentially plausible that women with CPS/DDR variants and thus a genetic background for neoplastic disease developed cancer in the wake of PPCM and heart failure.

These observations may well have far-reaching implications, not only for the understanding of the pathogenic mechanisms of PPCM and cancer development in patients with heart failure, but also for the clinical care of women with a history of PPCM or cancer who become pregnant. Despite small numbers, the data would support the close monitoring of left ventricular function in women with a history of cancer who become pregnant. Reciprocally, patients who develop PPCM should be followed up for the detection of cancer emergence. Would genetic screening then help to detect women at higher risk for PPCM and/or cancer? As proposed by Pfeffer et al. (5), the present finding of the high prevalence of variants for CPS/DDR and/or DCM/HCM needs to be confirmed in larger registries to strengthen their link with PPCM and/or cancer. Should this finding be confirmed, it would provide a strong incentive to introduce the aforementioned recommendations into guidelines for the clinical care of pregnant women at high risk for cancer and PPCM development.

ADDRESS FOR CORRESPONDENCE: Dr. Jean-Luc Balligand, FATH/IREC, Tour Laënnec +3, B1.57.04, 57 avenue Hippocrate, 1200 Brussels, Belgium. E-mail: jl.balligand@uclouvain.be. Twitter: @ClinUnivStLuc.

REFERENCES

1. Hilfiker-Kleiner D, Sliwa K. Pathophysiology and epidemiology of peripartum cardiomyopathy. Nat Rev Cardiol 2014;11:364–70.

2. Sliwa K, Hilfiker-Kleiner D, Petrie MC, et al. Current state of knowledge on aetiology, diagnosis, management, and therapy of peripartum cardiomyopathy: a position statement from the Heart Failure Association of the European Society of Cardiology Working Group on peripartum cardiomyopathy. Eur J Heart Fail 2010;12:767–78.

3. Liu S, Aghel N, Belford L, et al. Cardiac outcomes in pregnant women with treated cancer. J Am Coll Cardiol 2018;72:2087–9.

4. Meijers WC, Maglione M, Bakker SJL, et al. The failing heart stimulates tumor growth by circulating factors. Circulation 2018;138:678–91.

5. Pfeffer TJ, Schlothauer S, Pietzsch S, et al. Increased cancer prevalence in peripartum cardiomyopathy. J Am Coll Cardiol CardioOnc 2019;1:196–205.

6. Hilfiker-Kleiner D, Kaminski K, Podewski E, et al. A cathepsin D-cleaved 16 kDa form of prolactin mediates postpartum cardiomyopathy. Cell 2007;128:589–600.

7. Regitz-Zagrosek V, Roos-Hesselink JW, Bauersachs J, et al. 2018 ESC guidelines for the management of cardiovascular diseases during pregnancy. Eur Heart J 2018;39:3165–241.

8. Sajjad M, Fradley M, Sun W, et al. An exploratory study to determine whether BRCA1 and BRCA2 mutation carriers have higher risk of cardiac toxicity. Genes 2017;8:E59.

9. Shukla PC, Singh KK, Quan A, et al. BRCA1 is an essential regulator of heart function and survival following myocardial infarction. Nat Commun 2011;2:593.

KEY WORDS cancer, genetic predisposition, oncogenesis, peripartum cardiomyopathy