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EDITORIAL COMMENT

Galectin-3 and Risk for Cancer or Heart Failure

Does Sex Matter?*

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Although cancer and heart failure (HF) are leading causes of death and morbidity in developed countries, the number of cancer and chronic HF survivors is increasing, given advances in available screening, diagnostic, and therapeutic options. Cancer and HF are known to be closely related entities, characterized by a bidirectional relationship.[1] In fact: 1) a significant proportion of patients with cancer are predisposed to the development of cardiovascular disease because of cardiotoxicity linked to chemotherapy, immunotherapy, and radiation therapy; and 2) in addition to sharing several risk factors (ie, diabetes, obesity, hypertension, and smoking, among others),[2,3] circulating biomarkers associated with either cancer or HF play a role in both conditions, indicating the possibility of activation of common pathways.[4] This background has therefore encouraged interaction between cardiologists and oncologists with the goal of optimizing the management of patients with either disease.

The search for novel biomarkers as useful tools for diagnostic and prognostic goals in every diseased condition is a cornerstone of translational research. Galectin-3 (Gal-3) (a chimera-like lectin) emerges among biomarkers of interest in both clinical conditions; indeed, it plays a key role in the acute inflammatory process by regulating the activation, migration, and apoptosis of immune cells, assisting the acute response to infection and other inflammatory noxae.[5] It is also involved in chronic inflammation, by promoting fibroblast activation and the process of fibrogenesis.[5] Several studies have evaluated the role of Gal-3 in HF and cancer, as both diseases are closely influenced by the development of fibrosis. With regard to HF evolution, it has been studied both as a risk factor and as an effective biomarker in the context of fibrotic degeneration in the early stages of dilated cardiomyopathy,[6] as well as early identification of acute myocardial infarction and remodeling underlying the development of HF.[7] By interfering in the signaling pathway involved in collagen synthesis in vascular smooth muscle cells, which is stimulated by high aldosterone levels, Gal-3 promotes vascular fibrosis and cardiac remodeling.[8] Moreover, preclinical studies have demonstrated the effectiveness of combined aldosterone and Gal-3 blockade in reversing isoproterenol-induced left ventricular systolic dysfunction and preventing the development of myocardial fibrosis.[8]

An association between Gal-3 and cancerogenesis has been suggested, as it is involved in tumor cell transformation, migration, invasion, and metastasis,[4] playing relevant roles in cell proliferation, adhesion, differentiation, angiogenesis, and apoptosis in both normal and pathologic tissues. Furthermore, Gal-3 plays a role in the tumor microenvironment as an immunosuppressor, decreasing T-cell activation, and as promotor of tumor growth (particularly gastrointestinal tumors), favoring neoplastic transformation and metastasis.[4]

Nonetheless, it is still unknown if Gal-3 represents a biomarker able to predict the risk for either cancer or new-onset HF. In this issue of *JACC: CardioOncology*, van den Berg et al[9] report a post hoc analysis conducted in patients enrolled in the

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PREVEND (Prevention of Renal and Vascular End-stage Disease) study,[10] focusing on the predictive value of Gal-3 in identifying patients at risk for developing cancer or HF, as well as on the influence of sex on its prognostic ability. They found a significantly higher value of Gal-3 in women than in men, both at baseline and at 4-year follow-up (11 ng/mL vs 10.6 ng/mL and 11.7 ng/mL vs 11.3 ng/mL, respectively; $P < 0.001$), though the relevant observed increase in Gal-3 during follow-up was equally distributed across both sexes.[9,11] During a median 11.5-year follow-up period, the investigators found a higher incidence of new-onset cancer in the male population compared with women and demonstrated an independent association between elevated Gal-3 and all types of new-onset cancer in men only. Similarly, the development of new-onset HF was more frequent in men than in women, and increased Gal-3 was associated with HF development in men but not women.[9]

Although this paper presents an intriguing hypothesis and offers challenging findings, some limitations should be mentioned. First, the retrospective nature of this work limits the applicability of its findings. Their confirmation, in a prospective evaluation, would require consideration for various confounding factors that likely influence the predictive value of Gal-3, including: 1) the etiology of HF; 2) the incorporation of known Gal-3 inhibitors, such as pectin in the diet or mineral corticosteroid receptor blockers as HF and hypertension pharmacologic agents; 3) consideration of the prevalence of childbearing age in women; and 4) the use of hormone replacement therapy in postmenopausal women. In this respect, as there might be a direct influence of sexual hormones on Gal-3 during tumor pathogenesis,[12] the measurement of Gal-3 could have different implications in either sex, as a sex-specific influence on cardiac structural remodeling and therapy is recognized in cardiovascular disease.[13] Nonetheless, the small sample of women (n = 67) who developed HF limits the findings relative at the influence of sex on the significance of Gal-3. Future prospective studies should address another unmet relevant issue: the temporal correlation between the evidence of elevated Gal-3 levels and diagnosis of either new-onset malignancy or HF, which could favor routine clinical implementation of this biomarker. From a methodological perspective, a thorough echocardiographic evaluation using global longitudinal strain assessment would potentially detect a worse functional trajectory earlier, compared with the sole evaluation of ejection fraction as in this study, depicting a more precise correlation between Gal-3 elevation and cardiac dysfunction. Finally, cardiac troponins and B-type natriuretic peptides, among many biomarkers of cardiovascular pathology, have been evaluated for their potential in predicting either HF or cancer (eg, gastrointestinal and pelvic tumors) incidence,[14] as well mortality.[14] In this regard, future studies should address the issue of the additive independent value of Gal-3, compared with high-sensitivity troponins and N-terminal pro-brain natriuretic peptide, and their eventual increased predictive value, when used in combination.

In conclusion, the study by van den Berg et al[9] brings novel information regarding a possible differential role of Gal-3 in predicting cancer and HF development in male and female populations. Every novel marker proposed for a clinical purpose must hold a number of intrinsic characteristics: 1) it should be measurable and reproducible, with optimal sensitivity and specificity for a diagnostic assay; 2) there should be epidemiologic evidence of its presence in apparently healthy people before the event; 3) its association with the disease must be biologically plausible, strong, and graded; 4) it must increase our ability to predict the event (the association must be independent of established traditional risk markers in multivariable analyses); 5) though not essential, it should be possible to assess if the prognostic impact of the biochemical marker can be affected by therapeutic intervention, thus decreasing the occurrence of events; and 6) combinations of risk markers together should predict events better than either individually.[15] On the whole, Gal-3, on the basis of the present observations, does not meet all these prerequisites. Future prospective, well-designed studies are needed to confirm van den Berg's interesting hypothesis.

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