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EDITORIAL COMMENT

Chemotherapy-Induced Valvular Heart Disease*

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Radiation therapy has been a mainstay for treating lymphomas and can be curative in some lymphomas such as Hodgkin's disease. Long term follow-up studies have shown progressive valvular heart disease in some patients, especially those with mediastinal radiation that includes the heart. In addition, these studies have observed that chemotherapy, particularly with anthracyclines, seemed to increase the risk of valvular disease. A study from the Netherlands by Aleman et al. (1) showed that, in 1,474 Hodgkin's lymphoma 5-year survivors, after a mean follow-up of 19 years compared with the general population in the Netherlands, the incidence of myocardial infarction (hazard ratio [HR]: 3.6) and heart failure (HR: 4.9) were increased significantly. They also noted that the concomitant use of anthracycline chemotherapy in 29% increased the incidence of heart failure and valvular disease, but did not report on the use of anthracycline chemotherapy alone.

A Norwegian study that started in 1993 and was updated in 2009 studied 116 Hodgkin's lymphoma survivors at a mean of 10 years after radiation therapy and in some anthracycline therapy, and showed that 31% had moderate valve regurgitation (2). The subsequent follow-up of 51 of these patients at a mean follow-up of 22 years showed progressive valvular heart disease (3). In 33% of the patients with moderate regurgitation at the first study, progression to severe regurgitation or valve replacement had occurred. Also, 39% of these patients now exhibited aortic stenosis, some severe, that had not been observed in the original study group. Because 55% of the patients reported in 2009 had anthracycline therapy as well, they evaluated these patients separately and found that this chemotherapy was associated with increased left ventricular diastolic dimension and decreased wall thickness, but not aortic stenosis. Thus, they hypothesized that anthracycline toxicity to the myocardium leads to ventricular dysfunction and secondary or functional valve regurgitation.

This year, the group from the Netherlands reported on the cardiovascular disease risk of Hodgkin's lymphoma patients after 40 years of follow-up (median 20 years) in 2,524 patients treated with radiation and anthracycline containing chemotherapy and compared them with the general population (4). The cumulative incidence of heart disease was 50% and by age 60 years, 20% had coronary artery disease, 31% had valvular heart disease, and 11% had heart failure as first events (more than one-half had multiple events). Radiation therapy alone (27%) increased the risk of valve disease (HR: 6.6), coronary disease, and heart failure (both HR: 2.7), and risk increased with radiation dose to the mediastinum. In those treated with anthracycline-based chemotherapy alone (n = 169; 6.7%), there was a significantly increased risk of valve disease (HR: 1.5) and heart failure (HR: 3.0), but not coronary artery disease. Also, this effect was related to the dose of anthracycline chemotherapy. Although the echocardiographic methods included valve regurgitation and stenosis grading, these results were not provided in the manuscript or the electronic content. However, the authors hypothesized that valve disease may be due to heart failure and chamber dilation or possibly papillary muscle injury, which suggests that they primarily observed regurgitation. The strengths of this study were the up to 40-year follow-up, sufficient patients to analyze the anthracycline chemotherapy alone group, and the comparison with population controls.

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In this issue of *iJACC*, Murbraech et al. (5) assessed the prevalence and associated risk factors for valvular heart disease in a cross-sectional national study of all adult lymphoma survivors after high-dose chemotherapy containing an anthracycline and autologous stem cell transplantation from 1987 to 2008. Valve disease was determined by echocardiography and was defined as more than mild regurgitation or any stenosis. The 274 patients were compared with healthy age- and sex-matched controls. Mean follow-up after their lymphoma diagnosis was 13 years. In 35%, radiation therapy involving the heart was also given. Valve disease was present in 22% and in 87% it was regurgitation. Seven of the 9 with severe valve disease had aortic stenosis; 6 of these 7 also had radiation to the heart and in 5 it was high-dose radiation. Among those who only received an anthracycline, valve disease was seen in 17%, which was a 3-fold increase compared with the controls and in 13% aortic valve degeneration was observed as compared with 3% in controls. Interestingly, when mitral regurgitation was compared with controls, there was no difference, but aortic and tricuspid regurgitation were increased significantly in the anthracycline chemotherapy alone group. Ventricular size was increased and function was decreased compared with controls, but these differences were modest. Multivariate analysis of all patients showed that age >50 years, women, ≥3 lines of chemotherapy, and cardiac radiation were independent predictors of valve disease. In those treated by chemotherapy only age >50 years and ≥3 lines of chemotherapy were associated significantly with valve disease. The authors concluded that anthracycline-containing chemotherapy alone is associated with valvular heart disease due to valve degeneration.

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Although this is a cross-sectional study with no report of prior echoes, the data supporting the hypothesis that anthracycline containing chemotherapy can cause direct valve injury is compelling. First, they had a relatively large group that received anthracycline chemotherapy alone (n = 177) and they compared them with matched controls. The echocardiograms were read blindly. Both valve disease in general and valve degeneration were more common in the chemotherapy alone patients compared with controls. Ventricular function and left ventricular volumes were significantly different between chemotherapy patients and controls, but the changes were modest and of doubtful biologic significance, which suggests that myocardial toxicity was not the only explanation for the higher incidence of regurgitant valve disease in the chemotherapy alone group. Also, comorbidities that could explain valve disease risk were no different between the patients and controls. In addition, ≥3 lines of chemotherapy was an independent risk factor for valve disease in the chemotherapy group. Finally, there was an association between decreased left ventricular function and degenerative aortic valve disease in the chemotherapy group, suggesting that myocardial and valve injury parallel each other.

Direct drug-induced valve disease has been observed with agents that increase fibrosis and collagen deposition by stimulating a specific serotonin receptor in valve tissue (6). These drugs include ergot alkaloids such as methysergide and ergotamine, ergot-derived dopaminergic agonists such as pergolide and the recreational drug ecstasy, and drugs metabolized into norfenfluramine such as fenfluramine and dexfenfluramine. These drugs can produce valve thickening that resembles carcinoid heart valve disease. In the early stages, regurgitation is the dominant lesion, which has been reported to occur before valve thickening can be detected by transthoracic echocardiography. The problem with proving that valve regurgitation is due to these drugs is that it is common, especially as people age, and most patients studied do not have prior echoes. Should cancer chemotherapy join the list of drugs that can cause direct valve injury? There is no evidence to suggest a serotonin receptor mechanism for these long-term effects of chemotherapy. However, chemotherapy does have direct cellular toxicity in mature cells that do not divide frequently such as the myocardium. Perhaps valvular endothelium can be damaged as well, leading to scarring, leaflet retraction, and thickening, which could cause regurgitation and eventually stenosis. Further basic and clinical research need to be done to elucidate this intriguing concept. At this time, it seems prudent to consider valve disease in long-term lymphoma survivors whether they received radiation or chemotherapy or especially both at high doses as a young person (<25 years of age). Perhaps other newer chemotherapeutic agents known to cause myocardial injury will also have these long-term effects on heart valves.

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REFERENCES

1. Aleman BM, van den Belt-Dusebout AW, De Bruin ML, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;5:1878–86.

2. Lund MB, Ihlen H, Voss BM, et al. Increased risk of heart valve regurgitation after mediastinal radiation for Hodgkin's disease: an echocardiographic study. Heart 1996;6:591–5.

3. Wethal T, Lund MB, Edvardsen T, et al. Valvular dysfunction and left ventricular changes in Hodgkin's lymphoma survivors. A longitudinal study. Br J Cancer 2009;4:575–81.

4. van Nimwegen FA, Schaapveld M, Janus CP, et al. Cardiovascular disease after Hodgkin lymphoma treatment: 40-year disease risk. JAMA Intern Med 2015;6:1007–17.

5. Murbraech K, Wethal T, Smeland KB, et al. Valvular dysfunction in lymphoma survivors treated with autologous stem cell transplantation: a national cross-sectional study. J Am Cardiol Img 2016;9:230–9.

6. Andrejak M, Tribouilloy C. Drug-induced valvular heart disease: an update. Arch Cardiovasc Dis 2013;5:333–9.

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