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CLINICAL CASE CHALLENGES

Acute Heart Failure 29 Years After Treatment for Childhood Cancer

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Doxorubicin and other antitumor anthracyclines can cause cardiomyopathy and heart failure (HF) in a dose-related manner, with a cumulative dose of 400 mg/m^2 of doxorubicin equivalent associated with 5% risk of HF in adults; however, children and the elderly may develop HF after significantly lower doses (1).

Time from anthracycline exposure to clinical manifestation of HF can be highly variable. Some patients develop HF symptoms months or years after cancer treatment, whereas others become symptomatic only after decades. These findings denote that the manifestation of HF may be influenced by a number of modifiers (age at treatment, concomitant or sequential exposure to other cardiotoxic drugs, treatment-related procedures such as chest radiation or stem cell transplantation, pre-existing or developing cardiovascular morbidities such as hypertension or diabetes) (2). However, survivor-tailored surveillance plays an intuitive role in detecting and mitigating HF risk.

Here we describe the challenging case of acute HF in a long-term survivor of childhood cancer. Anthracycline dose and lack of survivor-tailored surveillance were characterized as important determinants of acute HF in this patient.

CASE PRESENTATION

A 37-year-old Caucasian man was admitted to our emergency department with a chief complaint of progressively worsening dyspnea over 2 weeks. He was normal weight and denied cardiovascular risk factors and a familial history of cardiomyopathy or sudden death. Recent viral infections were not noted.

At the age of 8 years, the patient had been admitted to another hospital and diagnosed with mediastinal diffuse large B cell non-Hodgkin lymphoma that was treated with 6 cycles of CHOP regimen (cyclophosphamide/doxorubicin/vincristine/prednisone, cumulative doxorubicin dose of 300 mg/m^2). Because of tumor refractoriness, the patient had then been treated with high-dose cytarabine in combination with the anthracycline-like anthracenedione, mitoxantrone. The latter was used at the cumulative dose of 30 mg/m^2, corresponding to 300 mg/m^2 of doxorubicin (assuming a 10:1 equimyelotoxic ratio of mitoxantrone to doxorubicin for comparisons between the 2 agents) (3). Salvage therapy with cytarabine-mitoxantrone was followed by autologous stem cell transplantation. Chest radiation was not included in tumor treatment. Cardiac follow-up with transthoracic echocardiography was conducted until the patient was 23 years of age. Records of cardiac follow-up were not available, but results were reportedly normal. No further cardiology follow-up was conducted over the 14 years preceding the acute HF presentation.

On admission, the patient was agitated, tachypneic, tachycardic, hypotensive (90/50 mm Hg), and oliguric. He exhibited jugular distension and pulmonary rales. Chest x-ray showed diffuse signs of alveolar pulmonary edema. The electrocardiogram showed sinus tachycardia (125 beats/min), nonspecific ST/T-wave abnormalities in the inferolateral leads, but not signs of acute myocardial ischemia. Transthoracic 2-dimensional

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echocardiogram showed biventricular severe systolic dysfunction (left ventricular ejection fraction [LVEF] 20%, tricuspid annular plane systolic excursion 10 mm, right ventricular fractional area change 26%), left ventricular (LV) dilatation (LV end-systolic volume of 81 ml/m^2), global hypokinesis, reduced wall thickness, mild-to-moderate increase of left atrium volume (84 ml), moderate functional mitral and tricuspid regurgitation, and an elevated estimated pulmonary arterial systolic pressure (65 mm Hg). Laboratory tests showed high levels of the N-terminal pro-B-type natriuretic peptide (NT-proBNP) (6,000 pg/ml, normal cut-off value of 150 pg/ml), slightly increased troponin I (0.560 ng/ml, normal cut-off value of 0.04 ng/ml), and a normal C-reactive protein. Bacterial, viral, and immunologic panels for acute myocarditis were negative.

ABBREVIATIONS AND ACRONYMS

HF = heart failure

LVEF = left ventricular ejection fraction

NT-proBNP = N-terminal pro-B-type natriuretic peptide

Pulmonary computed tomography angiography ruled out pulmonary embolism, and coronary angiography ruled out obstructive coronary artery disease. Cardiac magnetic resonance confirmed severe biventricular dysfunction with a diffuse reduction in cardiac mass and wall thickness, absence of late gadolinium enhancement (a marker of fibrosis) or edema on T2-weighted sequences, and absence of LV apical thrombus on early gadolinium enhancement sequences for microvascular obstruction. In light of these findings, common causes of acute HF (acute coronary syndrome; Takotsubo syndrome; pulmonary embolism; and viral, bacterial, or autoimmune myocarditis) were excluded. Familial dilated cardiomyopathy was excluded by subjecting the patient's parents (both age >60 years) and first-degree relatives to electrocardiography and echocardiography, which were normal. In light of the oncologic history of the patient, we considered anthracycline-related late-onset HF as the most plausible diagnosis (**Table 1** for the differential diagnosis). Possible interactions of anthracycline cardiotoxicity with underlying titin-truncating genetic variants were also considered, but were excluded based upon clinical considerations (4).

TABLE 1 Differential Diagnosis of Anthracycline-Related Cardiomyopathy Versus Other Clinical Conditions

Clinical Condition	Pros	Cons
Acute coronary syndrome	• Sudden presentation • Moderate troponin I elevation	• No chest pain • No dynamic ECG changes • No regional wall motion abnormality at echocardiography • Normal coronary angiogram • No LGE on CMR
Acute massive pulmonary embolism	• Acute presentation with worsening dyspnea • Moderate D-dimer elevation • Right ventricular dysfunction	• No right ventricular pressure overload on echocardiography • No ECG changes • Negative pulmonary computed tomography angiography
Takotsubo syndrome	• Sudden presentation • Moderate troponin I elevation • Significant NT-proBNP elevation • Normal coronary angiogram	• No emotional or physical stress • Low InterTAK score • No ECG changes • No typical apical ballooning on echocardiogram • No myocardial edema on CMR
Acute myocarditis	• Acute presentation with worsening dyspnea • Negative coronary angiography • Moderate troponin I elevation	• No recent history of fever or gastrointestinal or flu-like symptoms • Normal C reactive protein • Negative bacterial panel (haemophilus legionella, mycobacterium tuberculosis, mycoplasma, pneumo-coccus, staphylococcus, chlamydia) • Negative viral panel (adenovirus, coxsackie virus, Epstein-Barr virus, respiratory syncytial virus, hepatitis A-B-C, human immunodeficiency virus-1, influenza virus, parvovirus B19) • Negative immunologic panel (antifibrillary, anti-myolemmal, antiactin, antitropomyosin, antisarcolemmal) • No ECG changes • No edema and LGE on CMR
Familial dilated cardiomyopathy	• Dilated cardiomyopathy on echocardiography and CMR • No edema and LGE on CMR	• No familial history of cardiomyopathy or sudden death • Normal ECG and echocardiography in parents and first-degree relatives
Anthracycline cardiomyopathy	• High cumulative doxorubicin dose • Doxorubicin stress exacerbation by mitoxantrone and autologous stem cell transplantation • Dilated cardiomyopathy without edema and LGE at CMR • Lack of cardiology follow-up over the last 14 yrs	• No endomyocardial biopsy

CMR = cardiac magnetic resonance; ECG = electrocardiogram; LGE = late gadolinium enhancement; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

Inotropes (dobutamine, noradrenaline) and loop diuretics (furosemide) were used in the acute phase to achieve hemodynamic stabilization and diuresis. The patient was discharged after 12 days of hospitalization on medical therapy consisting of a beta-blocker (carvedilol), potassium-sparing diuretic (canrenone), and dual-acting neprilysin inhibitor/angiotensin receptor blocker (sacubitril/valsartan at a maximum tolerated dose of 49/51 mg twice daily). The NT-proBNP was 2,880 pg/ml at discharge. After 3 months of therapy, the patient was in New York Heart Association functional class I HF. Transthoracic echocardiography showed a significant improvement in LV and RV systolic function (LVEF 45%, right ventricular fractional area change 45%), with only mild mitral and tricuspid regurgitation. The NT-proBNP was 478 pg/ml. Similar echocardiographic findings were obtained at a recent 18-month follow-up visit, confirming a good response to carvedilol, canrenone, and sacubitril/valsartan.

DISCUSSION

We described the case of a seemingly healthy long-term survivor of childhood cancer with acute HF. Anthracycline-related late-onset HF was judged most plausible. We acknowledge that endomyocardial biopsy was not performed, but we emphasize that removal of damaged foci may occur over time, limiting the diagnostic power of endomyocardial biopsy in a long-term survivor. On a different note, lack of fibrosis at cardiac magnetic resonance could be consistent with the action of long-lived anthracycline hydroxymetabolites that do not necessarily cause necrosis/apoptosis with replacement fibrosis, but inhibit ion-dependent ATPases governing contractility and, eventually, cardiac mass (1).

Because our diagnosis was primarily one of exclusion, the oncologic history of this patient was scrutinized. The patient had been exposed to a cumulative anthracycline dose of 600 mg/m^2 (300 mg/m^2 of doxorubicin in front-line CHOP and 300 mg/m^2 of mitoxantrone-based doxorubicin equivalent in salvage therapy with cytarabine). The available evidence now shows that in survivors of any childhood cancer type, after adjusting for age at treatment and chest radiation, the probability of HF begins to increase after 100 to 150 mg/m^2 of doxorubicin equivalent and increases sharply after >250 mg/m^2 (5). In homogeneous cohorts of long-term survivors of childhood acute lymphoblastic leukemia, cardiomyopathy was relatively infrequent after <250 mg/m^2 of doxorubicin, but persistent depression of LV contractility was evident after >300 mg/m^2 (6). We conclude that a cumulative anthracycline dose of 600 mg/m^2 had exposed our patient to a high risk of anthracycline-related HF.

HF risk may have been further increased by interactions between different components of oncologic treatment. Mitoxantrone cardiotoxicity increases in patients with prior doxorubicin (7). Translational studies, mimicking sequential exposure of human heart to doxorubicin and mitoxantrone, now show that the 2 drugs engage in harmful interactions, with mitoxantrone causing its own mechanisms of toxicity while also aggravating those induced by prior doxorubicin (8).

These notions imply that sequential treatment with doxorubicin and mitoxantrone may have exposed our patient to a greater-than-additive cardiotoxicity. Anthracycline-related HF risk may have been exacerbated also by the autologous stem cell transplantation our patient received after doxorubicin- and mitoxantrone-based therapies (2).

We were unable to identify clinical events that precipitated acute HF after 29 years of seemingly healthy survival to cancer. Acute HF likely recapitulated a pathophysiological continuum that began with the first anthracycline administration, proceeded through a long asymptomatic phase of cardiac dysfunction, and eventually decompensated as cardiac reserve collapsed. Survivor-tailored surveillance would have been important during the asymptomatic phase to detect abnormalities in diastolic dysfunction or global longitudinal strain that precede LVEF decrements and might guide earlier initiation of HF therapy (9). Our patient did not participate in any survivor-tailored follow-up over the last 14 years. He received his first global longitudinal strain measurement during hospitalization, showing a remarkably altered value (−7%, compared with an institutional reference value of −19.9 ± 2%).

According to the International Late Effects of Childhood Cancer Guideline Harmonization Group, survivors treated with ≥250 mg/m^2 anthracyclines should receive surveillance with echocardiography within 2 years after treatment completion. Surveillance should be repeated within 5 years after cancer diagnosis and continued lifelong every 5 years (5). Both survivors and their providers should be aware of these recommendations, but our report illuminates how things can be different in real life. Cancer survivors are frequently entrusted to local providers unfamiliar with the intricate needs of this special population. On the other hand,

cancer survivors may have a limited awareness of the lifelong cardiovascular risk they are exposed to. Here, the survivor and his provider jointly assumed that cardiology follow-up and echocardiography could be safely discontinued 15 years after cancer treatment, leaving cardiomyopathy to progress in the following 14 years until acute HF eventually occurred. Data from the Childhood Cancer Survivor Study confirm that patients followed by a primary care clinician are less likely to receive echocardiograms compared with patients followed at a cancer center (10).

Once considered irreversible, anthracycline cardiomyopathy is now known to respond to modern HF therapy. Our patient continues to benefit from HF therapy that includes a newer therapy like sacubitril/valsartan. Given that HF therapy was started only after cardiomyopathy had progressed to the stage of decompensation, follow-up visits have been cautionary scheduled every 6 months to monitor its effects over time.

CONCLUSIONS

Considerations about anthracycline dose and insufficient surveillance were used to define anthracycline cardiomyopathy as the most plausible cause of acute HF in a long-term childhood cancer survivor. Response to HF therapy has been favorable but intensified follow-up is mandatory. Risk awareness and compliance with expert recommendations should help doctors and survivors prevent late cardiovascular sequelae of cancer therapy.

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