

Cardiogenic Shock 14 Years Post Anthracyclines

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Abstract

Significant advances in cancer treatment markedly improved survival rates of children diagnosed with cancer. However, chemotherapeutic or radiologic treatments might result in health consequences. For example, anthracycline agents were one of the most widely used chemotherapeutic drugs and known to cause cardiotoxicity.

We report on a 20-year old man with sudden onset of multi-organ-failure caused by a severe cardiogenic shock and the urgent need for implantation of a continuous-flow left ventricular assist device. Fourteen years before, he was diagnosed with childhood T-lymphocyte acute lymphoblastic leukaemia implying the application of the ALL-BFM-2000-protocol with a cumulative dose of 240 mg/m² of anthracycline (120 mg/m² daunorubicin + 120 mg/m² doxorubicin). Post-chemotherapeutic clinical monitoring lasted for two years till complete remission of leukaemia was diagnosed. Histology of intraoperatively taken endomyocardial biopsies showed an extensive fibrosis and vacuolated cardiomyocytes compatible with late-onset of anthracycline-induced cardiomyopathy. The patient recovered quickly and was discharged to rehabilitation 20 days after continuous-flow left ventricular assist device implant. Our case emphasized the need for consistent and detailed follow-ups to assess the global risk of premature cardiovascular disease prior to the development of congestive heart failure in cancer survivors of the childhood.

Keywords: Anthracycline; T-Lymphocyte Acute Lymphoblastic Leukaemia (T-ALL); Cardiomyopathy; Cardiogenic shock; Left ventricular assist device

Abbreviations: cLVAD: Continuous-Flow Left Ventricular Assist Device; cTnT: Cardiac Troponin T; EBV: Epstein-Barr Virus; INTERMACS: Interagency Registry For Mechanically Assisted Circulatory Support; LVSF: Left Ventricular Shortening Fraction; NT-proBNP: N-Terminal Pro-Brain Natriuretic Peptide; PCR: Polymerase Chain Reaction; T-ALL: T-Lymphocyte Acute Lymphoblastic Leukaemia

Introduction

Anthracyclines were commonly used in the anti-neoplastic treatment for childhood cancers [1,2]. Almost all children with common cancers and acute leukaemia (up to 94% [3]) were treated with anthracyclines. But there was no convincing evidence for a significant higher survival taking anthracyclines [4] compared to other chemotherapeutic drugs.

Among all chemotherapeutic drugs anthracyclines were probably the well-known initiator of cardiotoxicity with an incidence between 3% and 18% [5]. This was mainly caused by disrupting the DNA-structure leading to the cessation of cell function [6]. That could induce morphological changes in the cells such as cytoplasmic vacuolization [7,8] as well as a loss of myofilaments in cardiomyocytes [9] and an increase in the number of apoptotic cells [9]. These changes were associated with dramatically reduced levels of various proteins including the transcription factor GATA4 and myosin heavy chain [8] and it also caused accumulation of autophagic vacuoles [8].

Known risk factors for anthracycline-induced toxic cardiomyopathy were female sex [10], black race [11] and young age at diagnosis [5], as well as high dosage and cumulative doses [12].

Case Report

In September 2014, a 20-year old man was transferred to our hospital for rescue-therapy in a cardiogenic shock. In his past medical

history, he suffered from a T-Lymphocyte Acute Lymphoblastic Leukaemia (T-ALL) in the year 2000. Hereupon, an anthracycline-based therapy with curative intent was administered, according to the ALL-BFM-2000-study [13], combined with a cranial radiation (cumulative-dose: 12Gy). A pre-existing cardiac illness was not known, and his familial history for heart disease was negative, too. On the last visit of a cardiologist, nine years before cardiogenic shock in July 2005, echocardiography and electrocardiogram were normal. The time until this emergency he was in healthy condition without any cardiac symptoms.

At first, the patient complained about two weeks history of intermittent vomiting and increasing abdominal pain, which was stronger in standing position. Oral proton-pump inhibitors prescribed by the general practitioner did not affect the symptoms. Reaching the emergency ward he suddenly became dizzy with low blood pressure and tachycardia. Fast abdominal sonography ruled out any abdominal focus of his symptoms or abnormality but showed incidentally a highly reduced cardiac function. Echocardiography confirmed the diagnosis of heart failure by showing an enlarged left and right ventricle with a calculated left ventricular ejection fraction of 20%. Despite a moderately mitral regurgitation, no valvular dysfunction was detected. This result combined with a cardiogenic shock and nearly normal inflammatory

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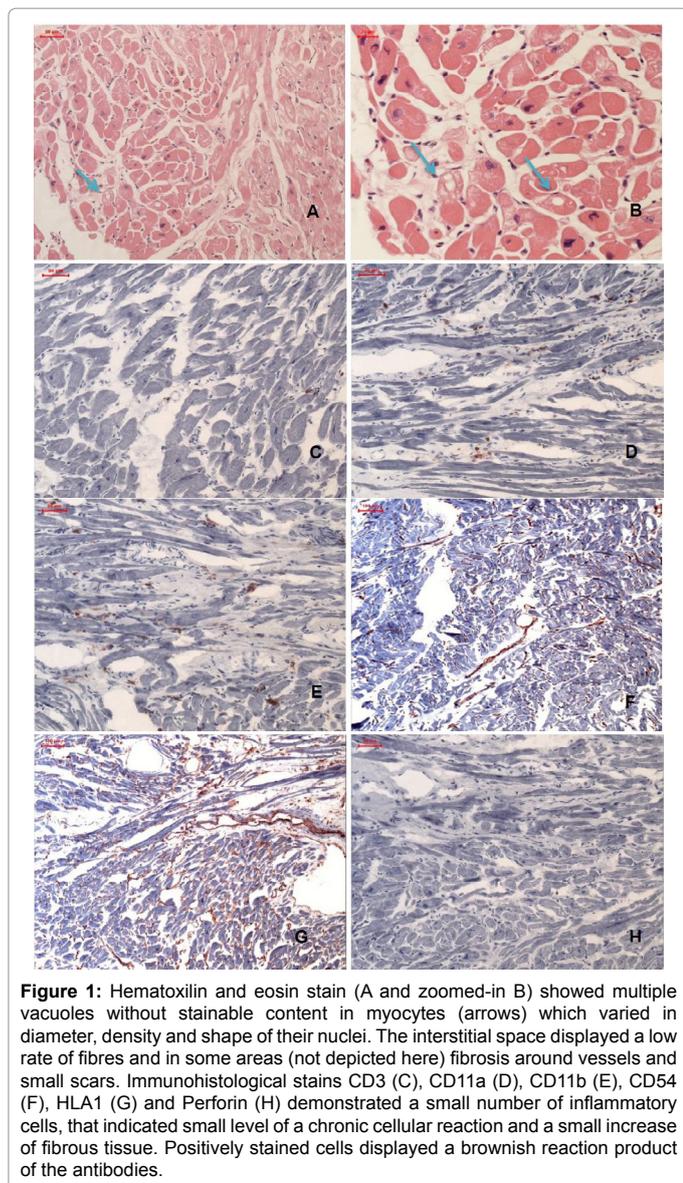


Figure 1: Hematoxylin and eosin stain (A and zoomed-in B) showed multiple vacuoles without stainable content in myocytes (arrows) which varied in diameter, density and shape of their nuclei. The interstitial space displayed a low rate of fibres and in some areas (not depicted here) fibrosis around vessels and small scars. Immunohistological stains CD3 (C), CD11a (D), CD11b (E), CD54 (F), HLA1 (G) and Perforin (H) demonstrated a small number of inflammatory cells, that indicated small level of a chronic cellular reaction and a small increase of fibrous tissue. Positively stained cells displayed a brownish reaction product of the antibodies.

parameters (CRP 10 mg/l and leucocytes 11.900/ml) made a gastrointestinal viral infection implausible. There was no anamnestic consumption of alcohol or drugs and moreover, acute infections or common cold in the recent past were not recognized by the patient. In consideration of his pre-existing diseases an anthracycline-induced cardiomyopathy seems most supposable.

Clinical examination (~100/min and ~85/45 mmHg) and laboratory diagnostics acknowledged the diagnosis of acute cardiogenic shock (NT-proBNP 14283 ng/l and cTnT 20 pg/ml, cvSO₂ 60%) with acute renal failure (creatinine 1.83 mg/dl) and congested liver (AST 68U/l, ALT 116U/l and GGT 78U/l). Therefore, rigorous treatment including catecholamines was immediately started. However, in spite of intensive medical treatment the multi-organ-failure was not possible to be stabilized. Consequently, the decision was made to implant a continuous-flow left ventricular assist device (cfLVAD, HVAD® from HeartWare) as a last resource. This was performed in a minimal-invasive surgery technique with two small mini-thoracotomies and partial sternotomy.

Intraoperative the macroscopically picture appeared as a dilated cardiomyopathy. Samples of the pericardium liquid did not prove any evidence of viral infection (PCR negative for adenovirus, influenza, mycoplasma pneumoniae, chlamydia trachomatis, EBV, enterovirus, mumps-virus and parvovirus) or bacterial infection (microscopic no bacteria after 48 hours). The myocardium biopsies did not show acute myocardial inflammation or necrosis on histology and immunohistochemistry. In contrast, an extensive fibrosis and vacuolated cardiomyocytes compatibly with a former damage were diagnosed – correlating with a late-onset of anthracycline-induced cardiomyopathy (Figures 1A-1H).

After successful surgical implant of the cfLVAD and a primarily prophylactic intracutaneous defibrillator to prevent ventricular arrhythmia, organ functions improved and the general state of health ameliorated appreciably. The right ventricular function represented itself as satisfactory. Twenty days after cfLVAD implantation the patient was discharged to a rehabilitation clinic.

Discussion

Our case emphasized the need for a consistent and detailed follow-up to assess the global risk of premature cardiovascular disease prior to prevent irreversible cardiac dysfunction [14], as it might arise in more than one third of these patients [15].

However, late-onset cardiomyopathy after more than one year was a rare complication 1.6% to 5% [16] but was regularly irreversible and in this context usually fatal [17]. Both the early- and the late-onset chronic progressive cardiotoxicity characteristically presented as dilated cardiomyopathy in adults [18]. The reason and the mechanism for a delayed onset as well as the molecular basis of memory of the applied dose were not known [19].

In general, cardiotoxicity was a dose-dependent consequence of chemotherapy. For anthracyclines cumulative doses of less than 240 mg/m² did not have direct toxic effects but might lead to subclinical cardiac alterations (reduced left ventricular shortening fraction), which were found in 30% of the patients [20]. Instead, cumulative doses of anthracyclines under 100 mg/m² were not known to be associated with late cardiac damage [21]. Therefore, we would recommend using lower doses in future cases, if there is any possibility.

Operative rescue-therapy with a cfLVAD was a rather new idea to deal with cases in which maximum medical treatment was not sufficient. Since low INTERMACS (Interagency Registry for Mechanically Assisted Circulatory Support)-levels 1+2 were attended by worst outcome [22], a primary implantation of a cfLVAD seemed justified in these cases of acute onset of heart failure in patients without a history of comorbidities. Similar cases had already been described in toxic cardiac shock cases [17,23,24]. Compared to these cases with an onset of five month to ten years, this patient had a very late onset of fourteen years until he had a cardiogenic shock.

Both researchers and clinicians agreed in a need of established guidelines to monitor cardiac function in children after cardiotoxic chemotherapy, but the most effective mode or frequency of monitoring were still not determined [25]. A good predictor for left ventricular decline was the left ventricular shortening fraction (LVSF). More than 50% of the patients showed a LVSF-decline of $-8.4 \pm 2.8\%$ from baseline to the post-treatment echocardiography [26]. An early decline directly after the end of anthracycline-treatment was associated with late-onset LVSF decrease after more than 12 years [27]. Promising biomarkers in children for monitoring cardiac function after treatment

with cardiotoxic chemotherapy were N-terminal pro-brain natriuretic peptide (NT-proBNP) [28] as well as cardiac troponin T (cTnT) [29], which were similarly used in regular heart failure clinics for progress-control.

Conclusion

A regular echocardiographic monitoring, as also advised by other cooperative groups [30], with measuring the LVSF should be established in all patients for at least 20 years after the last anthracycline therapy. Additionally, in children with anthracycline therapy a co-medication with cardioprotectors like dexrazoxane or carvedilol should be considered. Dexrazoxane acted by binding free iron or removing iron from anthracycline-iron complexes [31], without compromising the oncological efficacy, in particular in survivors of high-risk ALL [32]. Carvedilol offered cardiac protection by inhibiting reactive oxygen species [33,34]. The body configuration also seemed to influence the cardiotoxicity [35], as a high BMI (body fat >30%) was associated with a lower doxorubicinol, which was expected to contribute cardiotoxicity [36].

Moreover, in young patients with cardiogenic shock without comorbidities a primary mechanical circulatory support with a cfLVAD seemed justified regardless of the INTERMACS level.

Competing Interests

- St. S., N.H.T., M.R. and U.M.G. as well as S.B. have no competing interests.
- F.M.W. and M.J.B. received honoraria from HeartWare, Inc.
- T.D. received travel funds from HeartWare, Inc.
- H.R. has a consulting agreement with HeartWare Inc.

Authors' Contributions

- St. S wrote the manuscript and participated in the postoperative hospital care.
- N.H.T. is an oncologist and was responsible for the oncology care and prognosis statements.
- M.R. participated in the preoperative medical hospital care.
- F.M.W. was the surgeon, who implanted the LVAD.
- U.M.G. is the pathologist, who did the histological analysis (Figure 1).
- T.D. is also a surgeon implanting LVAD.
- S.B. has, as the chief cardiologist, a big expertise in heart failure-treatment and was revising the script critically for important intellectual content.
- H.R. has, as the chief physician, a great expertise in LVAD care and has revising the script critically for important intellectual content.
- M.J.B. helped writing the script and has given final approval of the version to be published.
- All authors read and approved the manuscript.
- All authors meet to the ICMJE-Guidelines.

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