



## Dilated Cardiomyopathy in a 25-Year-Old Patient as a Result of Radiation and Chemotherapy after Stem Cell Transplantation

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### Abstract

Dilated cardiomyopathy is a disorder characterized by chamber dilatation and cardiac dysfunction, which is not the result of an ischemic or valvular heart disease. The authors report the occurrence of dilated cardiomyopathy in an asymptomatic 25-year-old patient with a history of chemotherapy (Fludarabine and ATG- antithymocyte globuline) and radiation therapy prior to stem-cell transplantation for septic granulomatosis, which was diagnosed 10 years after transplantation. This proved to be refractory to the initiated medication and made the implantation of a CRT-D (cardiac resynchronization with defibrillation therapy) device necessary. The long-term outcome especially in young patients is unknown and the need for assist device or heart transplantation should be closely evaluated in case of further worsening of the cardiac function.

**Keywords:** Dilated cardiomyopathy; Chemotherapy; Fludarabine; ATG; Total body irradiation; Septic granulomatosis; Arterial hypertension; Cardiac resynchronization therapy

### Case Presentation

A 25-year-old man was admitted to the department of internal medicine in November 2014 for the management of a new diagnosed dilated cardiomyopathy with severely impaired ejection fraction. The patient was asymptomatic at the time of diagnose. His history revealed arterial hypertension, hyperlipidemia, overweight as well as septic granulomatosis (X-chromosomal hereditary). As a result of the septic granulomatosis he suffered from many episodes of *Aspergillus pneumonia* (in the Year 1996, 2000 and 2002), which led to resection of the left upper lobe (in the year 2000) and of the inferior left lobe of the lung (in the year 2002). Afterwards, the patient received in 2004 stem-cell transplantation. Before transplantation a conditioning treatment involving chemotherapy with Fludarabine, ATG (antithymocyte globulin) as well as total body irradiation was performed. The last cardiologic follow-up was performed in January 2014. Back then a stress test showed no sign for ischemia. Furthermore, the patient had a family history of cardiac disease (his uncle suffered from sudden cardiac arrest and his grandfather had a pacemaker). The patient denied using alcohol and drugs.

Actual physical examination revealed no signs of cardiac decompensation and the auscultation provided physiological murmur sounds. The ECG (electrocardiography) at admission revealed a sinus rhythm with narrow QRS complex. A transthoracic echocardiography showed an impaired ejection fraction at 22% with global hypokinesia. Furthermore, a diastolic dysfunction II° was reported (E>A, E/E' 10). The diameter as well as the volume of the left ventricle (65 mm, respectively 220 ml) were considerably above the normal range (36-54 mm, respectively <155 ml). The right ventricular function was slightly reduced (TAPSE 16 mm).The performed coronary angiography demonstrated a one-vessel coronary artery disease involving the left anterior descending artery, in which a drug-eluting stent was implanted. Because of the complex medical history and unclear etiology of the disease, we also performed a myocardial biopsy. The investigation revealed a chronic myocardial damage due to an incipient dilated cardiomyopathy. Furthermore, there were signs of a moderately active lymphocytic endocarditis without relevant inflammation in the heart muscle. The patient was discharged with dual antiplatelet therapy (ASS and Clopidogrel) for 12 months and optimized heart-failure therapy including an angiotensin-converting-enzyme inhibitor, a beta blocker as well as an aldosterone inhibitor. To prevent sudden cardiac arrest the patient received a Life Vest. Furthermore, in order to achieve a very close follow-up, the patient received telephone monitoring over our special ambulance for heart failure. This way the heart-failure therapy was

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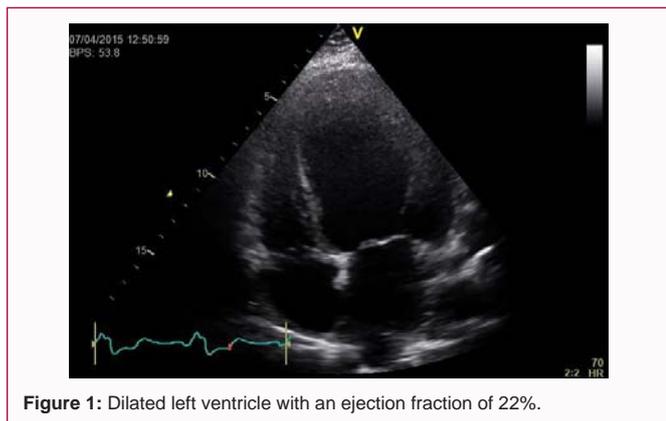


Figure 1: Dilated left ventricle with an ejection fraction of 22%.

safely further optimized. Ivabradine, an inhibitor of the funny channel, had to be discontinued because of adverse effects (burning sensation of the tongue). The echocardiography at the next follow-up in February 2015 revealed a minimal improvement of the ejection fraction (30%) with no significant changes in size or volume of the left ventricle (66 mm, respectively 233 ml). Furthermore, there was also a reduction of the NT-pro-BNP (brain-type natriuretic peptide) value from initially 4218 ng/l to 503 ng/l. Considering this slight amelioration, a reevaluation of the CRT-D (cardiac resynchronization with defibrillation therapy) was organized in 2 months. The patient had remained asymptomatic since admission. A genetic follow-up was realized to search for inherited dilated cardiomyopathy even though the results in April 2015 showed no evidence of mutations of the LMNA (Lamin A/C), MYH7 (cardiac beta myosin heavy chain), TNNT2 (cardiac troponin T) and MYBPC3 (cardiac myosin binding protein C) genes.

On the next follow-up in April 2015, the patient presented with a declined ejection fraction (EF 20%) as well as a higher NT-pro-BNP value of 1044 ng/l. The patient denied the occurrence of any new

symptoms. Considering the already optimized heart failure therapy and the new wide total left bundle branch block (QRS 150 ms) with pronounced asynchrony in the echocardiography, we decided to move forward with the cardiac resynchronization by defibrillation therapy (CRT-D), which was performed 3 weeks later. On the last follow-up in October 2016 the echocardiography revealed no relevant changes in size or volume of the left ventricle (65 mm, respectively 258 ml) despite the implantation of the CRT-D device with 100% biventricular stimulation. The ejection fraction remained severely impaired (EF 20%) and the NT-pro-BNP value was 893 ng/l.

In conclusion, after ruling out several other causes, we suspect that the performed chemotherapy and total body irradiation are the cause for the dilated cardiomyopathy in this very young patient.

### Discussion

Dilated cardiomyopathy is a disorder characterized by chamber dilatation, mostly left ventricle, and cardiac dysfunction, which is not the result of an ischemic or valvular heart disease. Despite elaborate investigations, in many patients there is no obvious cause for the disorder, which is why most of them are assigned the diagnosis of idiopathic dilated cardiomyopathy [1].

First of all, studies report several genetic mutations in a significant percentage of cardiomyopathies, such as sarcomere DCM genes (TNNT2,  $\beta$ -MHC, MYBPC3) which account for 35-40% of genetic dilated cardiomyopathy, as well as Z band proteins and costamere genes (MLP, CARP) or nuclear membrane defects in LMNA genes [2,3]. In our case the genetic investigation presented no evidence of mutations in the above mentioned genes making the familial dilated cardiomyopathy unlikely. Secondly, a relevant differential diagnosis could be arterial hypertension. Our patient received antihypertensive Therapy since 2005, but the myocardial biopsy showed no specific changes in this regard. Thirdly, another possible cause for the dilated cardiomyopathy could be represented by the chemotherapy or



Figure 2: Electrocardiogram shows a sinus-rhythm with a narrow QRS complex (ECG from above) and a wide total left bundle branch block (150 ms, ECG from below).

radiation therapies, both of which our patient received 10 years earlier. In long-time cancer-survivors with thoracic radiation, cardiovascular disease is one of the leading causes of mortality, especially when additional chemotherapy is performed. The side effects of the radiation occurs mostly 10 to 20 years after therapy. Radiation therapy leads to the generation of free radicals and DNA damage, leading to endothelial dysfunction of the microvasculature, thrombosis and small-vessel disease. Larger vessels, such as coronary arteries, can also be affected, leading to stenosis [4]. Typical atherosclerosis gets along only with intimal plaque formation, though, in radiation-induced coronary artery disease it also comes to thinning of the media and extensive adventitial fibrosis [5]. An approximate duration of 82 months to develop a radiation-induced coronary artery disease has been described [6]. Myocardial damage induces progressive fibrosis, diastolic dysfunction and finally restrictive cardiomyopathy [7]. Systolic dysfunction associated with radiation therapy alone, occurs in less than 10% of the patients [8,9]. The relative risk of coronary artery disease associated with radiation therapy increases with time after exposure, at 10 years the risk of ischemia, sudden cardiac arrest or heart failure is 2.9%, compared with 24.7% at 25 years [10]. This complication is usually asymptomatic and difficult to diagnose, as most of the patients do not experience any chest pain as a consequence of impairment from radiation injury to sensory nerves in the chest [11]. In our case, the patient denied angina.

Anthracycline-based chemotherapy and its cardiac toxicity are well known. However, there are many chemotherapeutic agents in which late cardiac complications have not been very well studied and described. Our patient was treated with fludarabine and anti-thymocyte-globulin (ATG). In this regard our search through the literature revealed no scientific evidence for cases of cardiac toxicity related to these two drugs and future investigations in this area would be required.

Lastly, autoimmune processes could play an important role in developing cardiomyopathies. Autoantibodies directed at heart cell receptors (muscarinic receptors, beta-adrenergic receptors as well as myocyte proteins) have been described in the literature, although the prevalence remains unclear [12]. The anti- $\beta$ 1-adrenergic receptor antibodies are suspected to promote cardiomyocyte apoptosis leading to cardiac remodeling [13]. In our patient, the tumor history including radiation and chemotherapy could have possibly triggered a production of auto-antibodies; still there have been no testing regarding this matter. Further studies in this area could raise awareness of the importance of testing for auto-antibodies, which could also improve the actual therapeutic strategies. In our case, the diagnosis was made in an already advanced stage. The pump function was refractory to medication, so that an additional therapy (cardiac resynchronization with defibrillation therapy) was performed. The long-term outcome is unknown, especially because of the young age, and the patient should be monitored very closely in order to initiate further investigations and therapy at an optimal time. At this moment we don't see the indication for an assist device or heart transplantation.

In summary we emphasize the importance of further and periodical evaluation, especially of young patients with a history of chemotherapeutic and radiation therapy, because of its insufficiently known side effects, especially its cardiac toxicity. Taking into consideration the well-established side effects of the radiation therapy we assume that an additional chemotherapy can aggravate and also accelerate the process of cardiac damage. Clinical examination and trans-thoracic echocardiography should be regularly performed, in order to early diagnose cardiac dysfunctions and allow proper treatment on time.

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