

DILATED CARDIOMYOPATHY IN TWO ADULT HUMAN IMMUNODEFICIENCY POSITIVE (HIV+) PATIENTS POSSIBLY RELATED TO HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART)

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Abstract: Human immunodeficiency virus (HIV) and acute immunodeficiency syndrome are known to be associated with cardiac involvement. In this respect, a relation between HIV and dilated cardiomyopathy has been described. Additionally, highly active antiretroviral therapy (HAART) may independently contribute to cardiac impairment.

We here report two cases of severely reduced left ventricular function detected in the context of a recent standardized screening of 132 HIV+ individuals of the German heart failure network.

Both patients presented in a poor overall condition and progressive exercise-induced dyspnea accompanied by edema or angina pectoris, respectively. Subsequent examinations revealed left bundle-branch blockade, ventricular arrhythmia, elevated serum BNP-levels as well as pathologic transthoracic echocardiography, left ventricular angiography, electron beam tomography and cardiac magnetic resonance imaging without significant coronary stenoses or immunohistological signs of an ongoing or prior myocarditis. Clinical signs of progressive chronic heart failure developed slowly but constantly following initiation of the HAART regimen.

Patients were treated by an implantation of a biventricular implantable cardioverter defibrillator beside conventional conservative standard therapy followed by a significant improvement of clinical symptoms. Antiviral medication could be maintained in both patients.

Taking all data into account, the diagnosis of a HAART-associated dilated cardiomyopathy could be assessed. Even though the pathogenesis of secondary heart failure after HAART is still object of investigation a mitochondrial impairment by antiviral drugs is thought to contribute the development of dilated cardiomyopathy. However, due to the coexistence of an eminent HIV infection, a direct effect of the HI virus itself can not be completely excluded.

Key words: HIV; HAART; cardiomyopathy; adverse events; biventricular implantable cardioverter defibrillator

INTRODUCTION

Highly active antiretroviral therapy (HAART) has substantially improved the survival of patients with human immunodeficiency virus (HIV) disease as well as acute immunodeficiency syndrome (AIDS) what resulted in a significant reduction of morbidity and mortality of HIV+ patients [15]. But prolonged survival of HIV+ individuals is also associated with an increase of adverse effects by the treatment itself [18].

An association between AIDS and dilated cardiomyopathy has been well-established. Even severe stages of cardiomyopathy represented by NYHA functional classes III-IV could be observed in a high number of patients especially in the pre-HAART era, although exact data are missing [2, 6, 9, 11]. Simultaneously, the use of antiretroviral drug therapy has been suggested to contribute to cardiac adverse effects including acute heart failure, chronic dilated cardiomyopathy, coronary heart disease and arrhythmias [1, 3, 5, 17].

A subsectional program of the German heart failure network ("Kompetenznetz Herzinsuffizienz") currently analyzes the primary prevalence of heart failure in HIV+ patients [8]. In this context, a total of 132 outpatient HIV+ individuals underwent a standardized examination program including patient history, clinical examination, electrocardiography (ECG), x-ray of the chest, 6-minutes-walk-test, brain natriuretic peptide (BNP) measurement and transthoracic echocardiography. We report two cases of severely reduced left ventricular function detected by echocardiographic screening.

CASE PRESENTATIONS

CASE 1

A 48-year-old HIV+ man (CDC/WHO C3, initial diagnosis 1995) presented with progressive exercise-induced dyspnea (NYHA III-IV), extensive central and peripheral edema and a poor overall condition. Patient history revealed interstitial plasma cell pneumonia, cytomegalovirus retinitis and colitis, infectious hepatitis B (anti-HBsAG 61 IU/L, anti-HBc positive) and renal in-

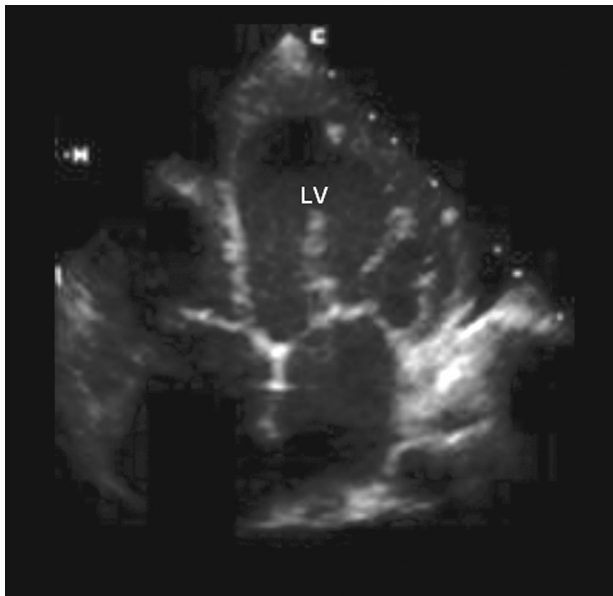


Fig. 1. Dilated left ventricle (LV) with a reduced shortening fraction confirmed by transthoracic echocardiography (4-chamber-view).

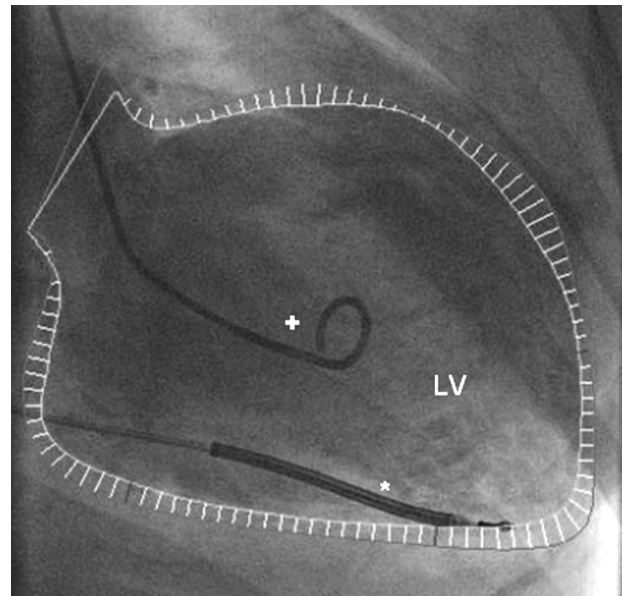


Fig. 3. Left ventricle- (LV-) angiography showing severely reduced left ventricular function (* = AICD lead, + = catheter, inner line = end-systolic volume, outer line = end-diastolic volume).

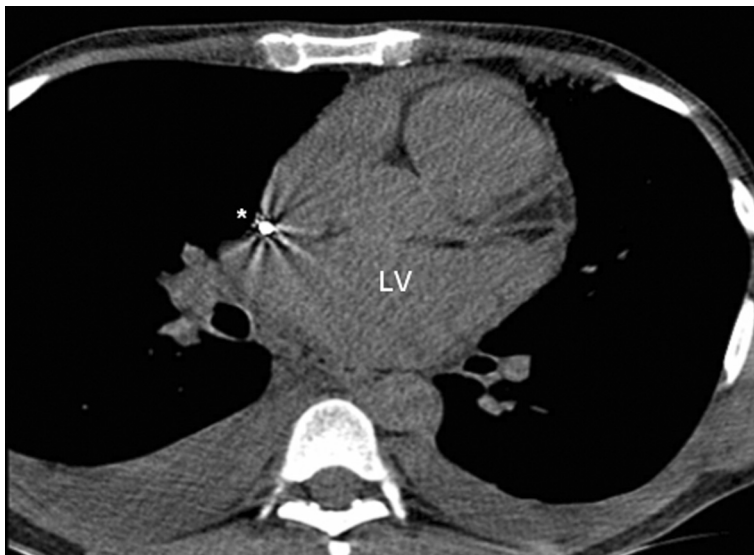


Fig. 2. Absence of coronary calcification in electron beam tomography (LV = left ventricle, * = AICD lead).

sufficiency after systemic antiviral cidofovir application. ECG obtained on admission disclosed a left bundle-branch block, echocardiography showed a left ventricular systolic dysfunction with an ejection fraction of 22% measured by multi-slice summation method (Fig. 1).

BNP levels (B-type BNP, Triage[®] BNP-Test, Biosite, San Diego, USA) were significantly elevated to a maximum of 1270 pg/ml (normal range <100 pg/ml). Electron beam tomography (EBT) showed no coronary calcium (EBT, Fig. 2), and coronary angiography revealed no significant coronary stenosis (catheterization, Fig.3).

Signs of a severe heart failure with a reduced left ventricular function could be confirmed. Myocardial biopsy unveiled hypertrophy, myocyte degeneration

and increased diffuse interstitial fibrosis. There were no direct signs of an ongoing myocarditis. Blood examination revealed an additional increase in serum lactate (max. 4.9 mmol/L, normal range 0.5 - 2.2 mmol/L). Prior therapy consisted of a combination of the nucleoside reverse transcriptase inhibitor combivir[®] (zidovudine 300 mg + lamivudine 150 mg, twice daily) and the protease inhibitor reyataz[®] (atazanavir sulfate 400 mg, once daily) since the beginning of 2004 resulting in a stable immunologic and virologic outcome (periodical virologic controls performed).

Taking all clinical and laboratory data as well as pathological and histomorphological results into account, the diagnosis of a HAART-associated dilated cardiomyopathy could be assumed.

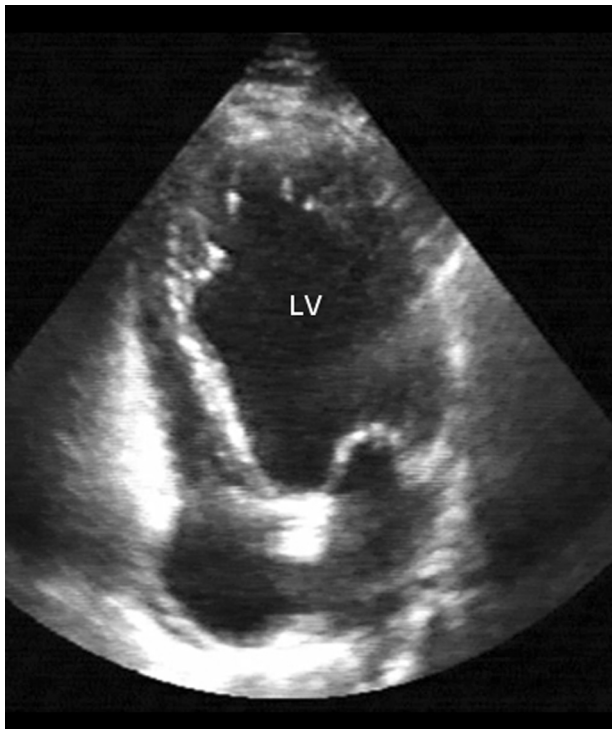


Fig. 4. Highly reduced ejection fraction associated by a significant dilatation of the left ventricle (LV) in echocardiography (4-chamber-view).

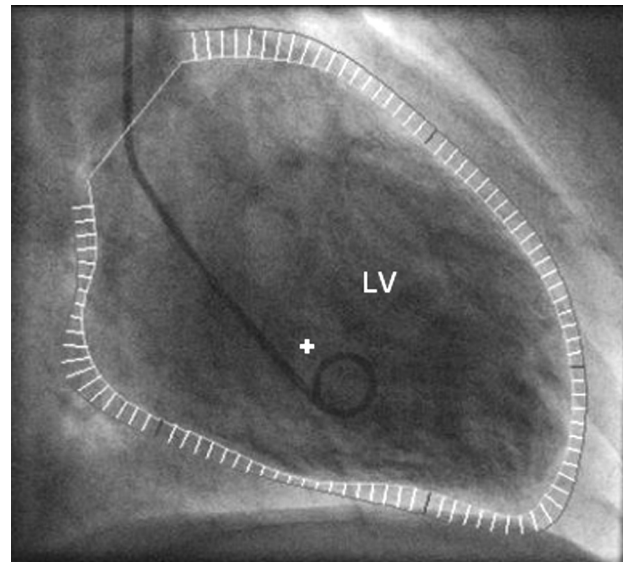


Fig. 5. Left ventricle- (LV-) angiogram revealed a significant decrease of the ejection fraction (+ = catheter, inner line = end-systolic volume, outer line = end-diastolic volume).

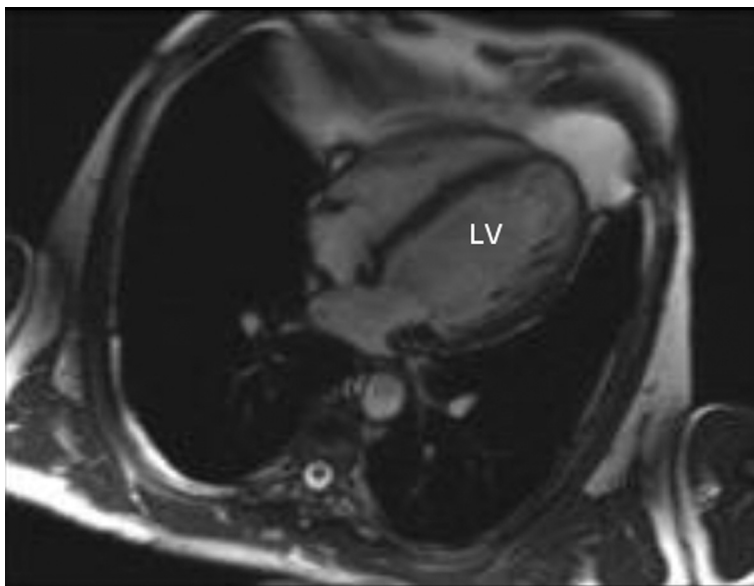


Fig. 6. Cine true MR imaging demonstrated similar results as compared to echocardiography with a largely dilated left ventricle (LV) accompanied by a highly decreased ejection fraction (4-chamber-view)

In the meantime, genotypic resistance analysis was performed during a short interruption of ongoing HAART. Due to limited treatment options with respect to the obtained resistogram in this patient we were not able to discontinue current HAART. As encouraging results in HIV- individuals exhibiting severe dilated cardiomyopathy exist we decided to implant a biventricular implantable cardioverter defibrillator (bivent-AICD) in addition to conservative standard therapy (digitalis, furosemide; ACE inhibitors and beta-blockers not possible due to symptomatic hy-

potension and renal failure). Shortly after implantation, the patient experienced a significant improvement of clinical symptoms combined with an increase of the ejection fraction to $> 25\%$.

CASE 2

A 51-year-old HIV+ man (CDC/WHO B3, initial diagnosis 1998) presented with progressive angina pectoris (CCS II), exercise-induced dyspnea (NYHA II-III) and lymphadenopathy. ECG on admission showed

normal sinus rhythm with a left bundle-branch block, 24 hour Holter monitoring revealed ventricular arrhythmia with a high number of ventricular premature beats, couplets and triplets. In echocardiography a severely dilated left ventricle with a highly reduced ejection fraction of 28% beside a global left ventricular hypokinesia could be observed (Fig. 4).

BNP levels were increased to a maximum of 339 pg/ml (normal range < 100 pg/ml). Serum lactate was within the normal range (1.2 mmol/L). Significant coronary stenosis was excluded by heart catheterization (catheterization, Fig. 5), although there was evidence of severe heart failure (MRI, Fig. 6).

Myocardial biopsy could confirm myocardial fiber hypertrophy and myocyte degeneration without any signs for acute or chronic myocarditis. Therapy consisted of a combination of the nucleoside reverse transcriptase inhibitor combivir[®] (zidovudine 300 mg + lamivudine 150 mg, twice daily) and the protease inhibitor viracept[®] (nelfinavir 750 mg, thrice daily) since the initial diagnosis. Considering the above-mentioned results, the hypothetic diagnosis of a HAART-associated dilated cardiomyopathy was set up.

Similar to the first case presented, due to the resistogram (genotypic resistance analysis) and the benefit of the virologic status (periodical virologic controls performed) achieved by the current regimen we decided not to substitute the ongoing medication. Taking the complex ventricular arrhythmias as well as the decreased ejection fraction of the left ventricle in account, we finally decided to implant a biventric AICD in order to improve clinical symptoms of heart failure in addition to conservative standard therapy (aldosterone receptor blockade, ACE inhibitor, beta-blocker, amiodarone).

DISCUSSION

As the prognosis of HIV+ individuals continuously improves following the introduction of HAART, potential adverse long-term effects are getting more and more eminent [10]. The chronic HIV infection alone is a well-established risk factor of dilated cardiomyopathy (prevalence about 3.6 %) [4]; nevertheless the occurrence of HAART-associated acute and chronic heart failure has also been reported [12, 16, 17, 19]. The pathogenesis of secondary heart failure following HAART is still poorly understood. However, mitochondrial dysfunction due to the inhibition of the mitochondrial polymerase gamma by the NRTIs, such as it has been found in skeletal muscle myopathy, has been proposed [7]. Studies performed in transgenic mice suggest that antiretroviral regimens are associated with diffuse destruction of cardiac mitochondrial ultrastructures and with an inhibition of mitochondrial DNA replication [13]. Additionally, the rare condition of NRTI-mediated lactic acidosis (0.3%) related to mitochondrial dysfunction is thought to further contribute to myocardial cell dysfunction [14].

In our patients, clinical signs of progressive chronic heart failure developed slowly but constantly following initiation of the HAART regimen, leading to the diagnosis of a HAART-associated dilated cardiomyopathy. A possible ischemic origin could be ruled out by coro-

nary catheterization. However, due to the coexistence of an eminent HIV infection, a direct AIDS-related cardiomyopathy or a component of AIDS-related heart failure can not be completely excluded. Case reports suggested a correlation between the discontinuation of the HAART regimen and an improvement of at least acute cardiac dysfunction [19]. As the resistograms showed a resistance against most of the current therapeutics, we were unfortunately not able to discontinue present antiviral medication in both of the patients. Therefore, in the presence of a significantly decreased left ventricular function, left-bundle-branch block and coexisting complex ventricular arrhythmias we decided to implant a biventric AICD in addition to conventional oral medication, resulting in good compliance and positive clinical outcome.

Consequently, even though HIV infections may be directly related to cardiomyopathy, also HAART regimen may cause dilated cardiomyopathy both in AIDS-related acute and chronic heart failure. In case of a resistance against potential alternative medications the implantation of a biventric AICD seems to be a successful alternative in order to stabilize or even improve clinical symptoms.

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