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Case Report

A young male patient with cardiomyopathy associated with human immunodeficiency virus infection in the era of highly active antiretroviral therapy

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ABSTRACT

Background: Cardiomyopathy in young people, especially those associated with HIV infection, has been reduced since the era of Highly Active Antiretroviral Therapy (HAART). In the era of post-HAART, manifestations of human immunodeficiency virus (HIV)-associated cardiomyopathy with impaired left ventricular (LV) systolic function are approximately about 1-3% of HIV-infected people. In this case, we presented how to diagnose and appropriately manage such a patient.
Case Illustration: A 27-year-old male patient who works as a health worker came to the emergency room with complaints of shortness of breath; it worsened in the last 2 weeks. He got vital signs: blood pressure 97/60 mmHg, heart rate 118 bpm, respiratory rate 23 tpm, and oxygen saturation 99 % with oxygen supplementation of 8 lpm. Risk factors in patients such as smoking, family history, hypertension, diabetes mellitus, and dyslipidemia were denied. He was diagnosed with HIV on (antiretroviral therapy) ART 3 years ago with risk factors for free sex without protection. The last CD4 value was 796 cells/ul (normal value 637 – 1485). The echocardiography showed all chamber dilatation, global hypokinetic, and a significant decrease in LV systolic function (LVEF 16%). Laboratory examination showed an increase of N-terminal prohormone of brain natriuretic peptide (NT-proBNP) into 6824 pg/mL (normal value <85.8). It was then treated by optimizing HF therapy continue HIV therapy.
Conclusion: In HIV patients who have fallen into heart failure, a proper diagnosis using relevant tools could be a reference for clinicians to make the right decision. Prompt treatment combination of optimal HF therapy and HIV therapy are becoming the keys to the treatment.

1. Introduction

Human Immunodeficiency Infection Virus (HIV) is one cause of occurrence of heart disease acquired and often symptomatic heart failure due to cardiomyopathy dilation. Complications of HIV infection against the heart have tendencies to occur slowly accordingly or development of HIV disease associated with therapy and infection other accompaniments.[2] According to the European Society of Cardiology (ESC), cardiomyopathy is defined as "a disorder of the myocardium in which structural or functional abnormalities are found in the heart muscle, without coronary artery abnormalities, hypertension, valvular heart disease, and congenital heart disease comparable to acquired myocardial abnormalities." According to ESC, the definition is seen as more practical in everyday practice. In the era of post-HAART, manifestations of HIV-associated cardiomyopathy with impaired left ventricular (LV) systolic function are approximately about 1-3% of HIV-infected people.[3]

2. Case Illustration

A 27-year-old male patient who works as a health worker came to the emergency room complaining of shortness of breath; it happens with light activity and has worsened in the last two weeks. The shortness of breath was accompanied by orthopnea and leg edema. He also complained about intermittent cough two weeks before admission with whitish sputum, but it was not accompanied by fever. He came to the emergency room with hemodynamically stable. From the physical examination, the vital signs were blood pressure 97/60 mmHg, heart rate 118 bpm, RR 23 tpm, and peripheral oxygen saturation 99 % with a simple mask 8 lpm. Ictus cordis palpable at ICS VI at 2 cm from the left midclavicular line. A bilateral mix of rhonchi was found on auscultation. Risk factors in patients such as smoking, family history, hypertension, diabetes mellitus, and dyslipidemia were denied. He was diagnosed with HIV on ART 3 years ago with risk factors for free sex, changing partners a lot, and without protection. From chest x-rays, there is cardiomegaly with congestive pulmonum and bilateral pleural effusion. Infiltrates are also seen in the lower right and left lung fields. The last CD4 value was 796 cells/ul (normal value 637 – 1485). The echocardiography showed all chamber dilatation, global hypokinetic, and a significant decrease in LV systolic function (LVEF 16%). Laboratory examination showed an increase of NT-proBNP into 6824 pg/mL (normal value <85.8). The patient was then treated by optimizing HF therapy in collaboration with internal medicine to continue HIV therapy in the patient.

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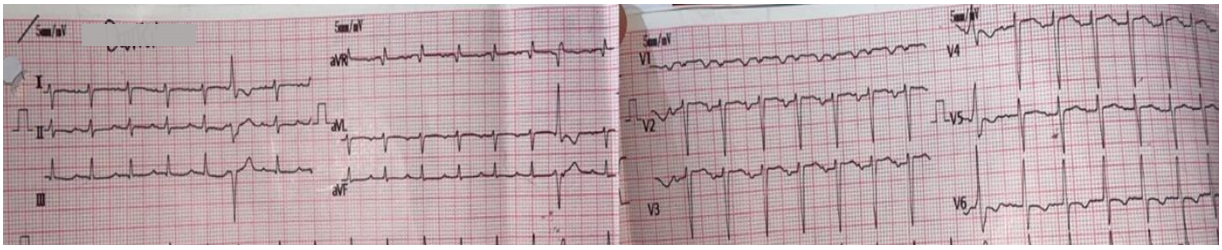

Figure 1. ECS shows sinus tachycardia with left atrial enlargement, left ventricular hypertrophy, and premature ventricular complex.

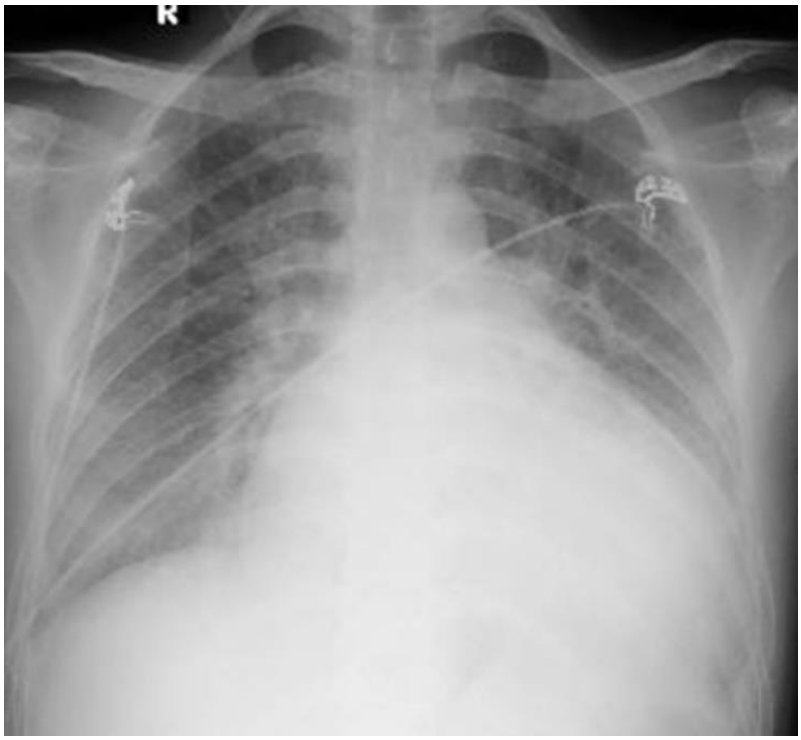

Figure 2. Chest X-ray shows cardiomegaly with pulmonary congestion and pneumonia.

3. Discussion

According to the American Heart Association (AHA), cardiomyopathies are defined as "a heterogeneous group of diseases associated with mechanical and/or electrical dysfunction that usually (but not always) has abnormal ventricular hypertrophy or dilatation and is due to a variety of causes, primarily genetic. Cardiomyopathy can be a disease that is present in the heart alone or is part of a systemic disease, often causing cardiovascular death or disability related to progressive heart failure. Meanwhile, according to the European Society of Cardiology (ESC), cardiomyopathy is defined as "a disorder of the myocardium in which there are structural or functional abnormalities in the heart muscle, without evidence of coronary artery abnormalities, hypertension, valvular heart disease, and congenital heart disease comparable to acquired myocardial abnormalities. According to ESC, the definition is seen as more practical in daily practice.[3]

According to ESC, cardiomyopathy is divided into five phenotypes: hypertrophic cardiomyopathy (HCM), dilated cardiomyopathy (DCM), arrhythmogenic right ventricular cardiomyopathy (ARVC), restrictive cardiomyopathy (RCM), and cardiomyopathy, which is not classified (unclassified). Each is divided into familial or acquired, then grouped again whether the cause is idiopathic or known. From the ESC classification, cardiomyopathy in patients with HIV is classified as acquired dilated cardiomyopathy.[2]

Pathogenesis

Cardiomyopathy in people living with HIV/AIDS is caused by various factors: HIV, myocarditis, drugs, and nutritional status.

The role of the HIV

Although it does not have a $CD4^+$ receptor, in several studies, HIV is suspected to be found in myocardial cells. Conducting in situ hybridization tests to detect HIV in the hearts of 22 patients who died of AIDS, the results found HIV nucleic acid signals in 6 patients suspected to be in the myocardium. There are found positive HIV hybridization signals in the myocardium of 58 of 76 patients with dilated cardiomyopathy, and no hybridization signals were found in controls.[4]

Studies using the in-situ hybridization technique have the disadvantage that it is difficult to distinguish with certainty whether the signal originates from myocardial cells or not. While no studies on humans have been enlightening, a study on primates infected with Simian Immunodeficiency Virus (SIV) found many similarities to HIV in humans. It is known that the SIV virus is not found in myocardial cells but rather in inflammatory cells that have $CD4^+$ receptors, such as lymphocytes and macrophages that surround the myocardium. This is confirmed by in-vitro studies conducted by Rebolledo et al. in human fetal myocyte cultures where HIV cannot infect myocytes. A hypothesis predicts that HIV causes changes in helper T lymphocyte function, which causes hypergammaglobulinemia, resulting in uncontrolled myocardial inflammation. Autoimmune factors may also play a role. HIV may cause damage to the myocyte cell surface, resulting in protein exposure, which then induces the emergence of autoantibodies. The patients with HIV and cardiomyopathy had higher levels of anti-a myosin autoantibodies than people living with HIV without cardiomyopathy. High anti-a myosin levels are also associated with shorter survival. Another theory emphasizes the role of gp120 glycoprotein in the occurrence of myocardial damage. Besides being

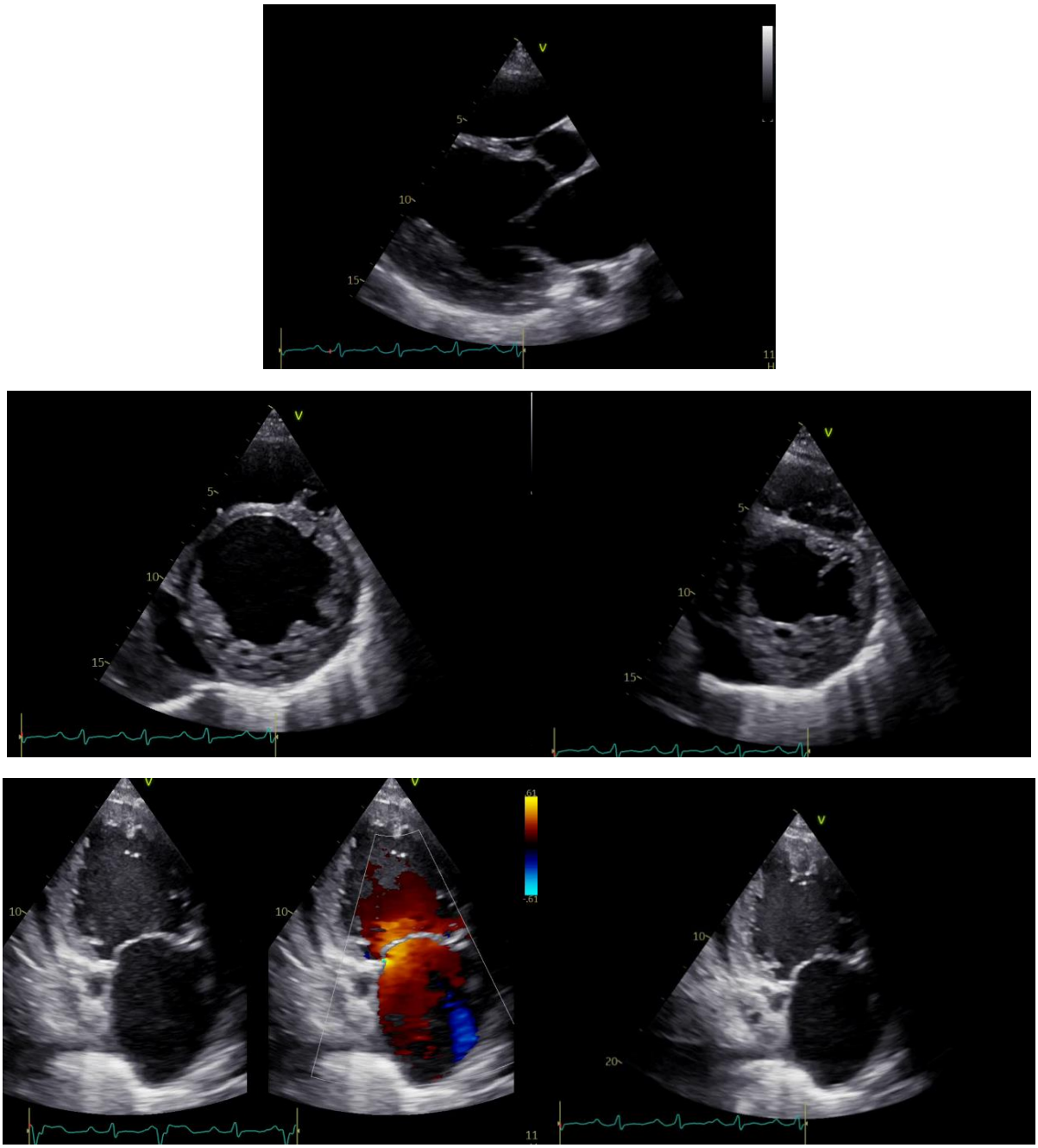

Figure 3. Echocardiography shows all chambers dilatation with global hypokinetic, low left ventricular ejection fraction, suspecting left ventricular non-compaction.

able to bind to the $CD4^+$ receptor, gp120 can bind to the chemokine receptor 4 (CXCR4) found in human cardiac myocytes. 20 Upon binding to CXCR4, gp120 can activate p38 MAP (mitogen-activated protein) kinase. 20–21 p38 MAP kinases are part of a group of intracellular enzymes that phosphorylate proteins in response to inflammatory mediators (e.g., cytokines) and stress (e.g., ischemia). Activation of p38 MAP kinase is associated with ischemia, hypertrophy, apoptosis, and impaired adrenergic signaling in cardiac myocytes. Gp120 also causes reduced myocyte contractility. Continuous infusion of gp120 in rats initially increased contractility, but a decrease followed (Figure 2). This may be due to the activation of p38 MAP kinase, which causes the release of Ca++, which increases contractility, but prolonged activation causes apoptosis.[5] P38 MAP kinase causes activation of iPLA2 (calcium–independent phospholipase A2) and troponin I phosphorylation. Substances that inhibit CXCR4, p38 MAP kinase, iPLA2, and troponin I phosphorylation in an experiment abolish the negative inotropic effect of gp120.[5]

As discussed above, cytokines can cause activation of p38 MAP kinase. In patients with HIV, there is an increase in pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6. These cytokines will cause an increase in inducible nitric oxide synthase (iNOS) through activation of p38 MAP kinase and nuclear factor kappa B (NFkappaB). High concentrations of NO can cause cardiac myocyte apoptosis. Apoptosis is closely related to cardiomyopathy. An autopsy study found in HIV patients with cardiomyopathy found increased elements that play a role in the occurrence of apoptosis in macrophages and myocytes compared to HIV patients without cardiomyopathy.[5]

Myocarditis

The incidence of myocarditis in autopsy studies is less–approximately one-third of all AIDS patients. A specific cause is found in less than 20% of these patients. Common pathogens in AIDS myocarditis include Toxoplasma gondii, Mycobacterium tuberculosis, and

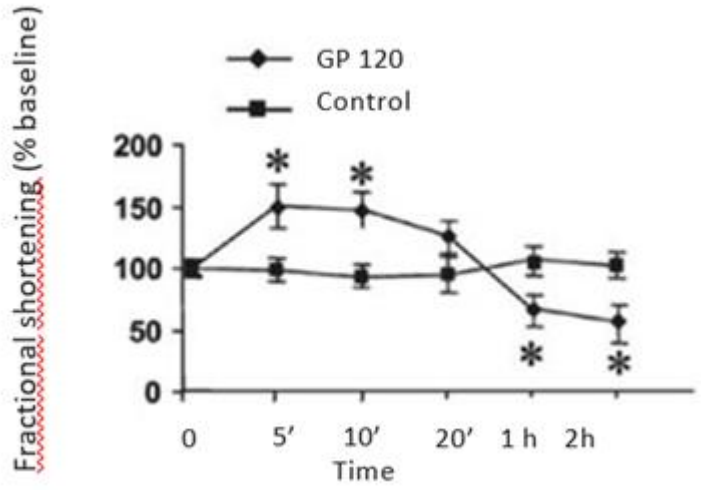

Figure 4. Effect of gp120 infusion on myocyte contractility represented by fractional shortening.[5]

Cryptococcus neoformans. Other organisms that are also found are Mycobacterium avium intracellulare complex, Aspergillus fumigatus, Candida albicans, Histoplasma capsulatum, Coccidioides immitis, cytomegalovirus, and herpes simplex. The HIV itself is also known to cause myocarditis. Because $CD4^+$ receptors are not found in cardiac myocyte cells, it is suspected that there is a role for other viruses, such as the Ebstein–Barr virus, in causing damage to myocytes and facilitating the entry of the HIV.[6]

Meanwhile, pathologically, the most common type of myocarditis is lymphocytic myocarditis. There are three histological features: lymphocytic infiltrate with myocardial fiber necrosis, lymphocytic infiltrate without myocardial fiber necrosis, and mild, focal myocarditis with mononuclear infiltrate.[1]

Reilly et al. studied the relationship between clinical and histopathological cardiac findings. In all patients who had clinical congestive heart failure, left ventricular dysfunction, or ventricular tachycardia (VT), myocarditis was found for pathological examination. Whereas in patients without myocarditis, none of them had clinical congestive heart failure. So, it was concluded that myocarditis is associated with clinical heart abnormalities that are more severe.[7]

In animal models, it is known that chronic phase myocarditis can lead to dilated cardiomyopathy. In the subacute phase, the virus levels in myocytes decreased, but the infiltration of mononuclear cells increased. This may be due to the presence of viral nucleic acid in myocytes or due to an autoimmune process.[7] Apart from being a pathogen, myocarditis in HIV can also occur in patients with immune reconstitution syndrome. Rogers et al. reported that a patient on HAART treatment for five weeks came with recurrent VT and then died. Autopsy showed lymphocytic infiltrate and myocyte necrosis of the heart.[1]

Drugs

Patients with HIV/AIDS tend to be exposed to a variety of drugs that can affect the heart. Some sufferers have a lifestyle that is close to alcohol and drugs. Long-term ethanol consumption can cause left ventricular systolic or diastolic dysfunction. Diastolic dysfunction is usually seen in heavy drinkers and is caused by myocardial interstitial fibrosis. Systolic dysfunction can be found even in people who consume small amounts of ethanol, such as social drinkers. Increased consumption in the long term will cause dilated cardiomyopathy and heart failure. In countries with high alcohol consumption, alcohol accounts for half of all dilated cardiomyopathy. The average man with dilated cardiomyopathy consumes 80 g of ethanol per day for more than five years. Cessation of ethanol consumption can improve systolic and diastolic function; the earlier, the greater the benefits. Cocaine can cause dysfunctional left ventricular systole by several mechanisms: ischemia and infarction, prolonged stimulation of the sympathetic system, increasing the production of reactive oxygen species, altering cytokine production, increasing gene transcription, causing changes in myocardial collagen and myosin, and inducing apoptosis. Cocaine can also cause acute ventricular dysfunction or transient apex ballooning (takotsubo cardiomyopathy or broken heart syndrome). Methamphetamine (shabu), both used intravenously and inhalation, has also been reported to cause cardiomyopathy.[8]

Treatment with antiretrovirals (ARVs), especially the nucleoside reverse transcriptase inhibitor (NRTI) class, is associated with the occurrence of cardiomyopathy. NRTIs cause or contribute to cardiomyopathy via mitochondrial toxicity by inhibiting mtDNA replication, namely DNA polymerase−œ. Reduced mtDNA replication leads to a lack of energy and oxidative stress. One of the NRTIs that is often associated with cardiomyopathy is zidovudine (AZT). AZT is known to reduce mtDNA replication, cause mitochondrial skeleton myopathy in a dose-dependent manner, and affect mitochondrial oxidative metabolism, ultimately reducing muscle contraction energy. A study conducted by Purevjav et al. demonstrated that myocardium expressing Fas ligand is more susceptible to AZT-induced dilated cardiomyopathy due to activation of the apoptotic pathway that causes myocardial dilatation and dysfunction. Dilatation causes acute heart failure. This may be due to a heart with cardiomyopathy depending on glucose transported via GLUT4 as an energy source, unlike a healthy heart, which can use various energy sources.[2] Other drugs are often used in patients with HIV/AIDS and can cause toxicity to the heart. However, not all of these drugs are associated with cardiomyopathy.[2]

Nutritional status

HIV/AIDS patients with dilated cardiomyopathy are associated with a lower body mass index (BMI) than patients without cardiomyopathy who have comparable CD4s and viral loads.[3] Selenium deficiency is also associated with cardiomyopathy. Selenium is required for the activity of the glutathione peroxidase enzyme. Selenium deficiency is associated with myopathy, cardiomyopathy, and immune system dysfunction including impaired phagocytic function and reduced CD4 cells. A study in Africa showed that selenium deficiency is found more frequently in HIV patients with cardiomyopathy.[4]

Clinical presentation

Patients with cardiomyopathy may be asymptomatic or present with overt heart failure. In HIV/AIDS patients, pulmonary infections, anemia, malnutrition, or malignancy are common, which can obscure the clinical heart failure.[3] This patient complained of shortness of breath, which happens with light activity and worsened in the last two weeks. The shortness of breath was accompanied by orthopnea and leg edema. This condition was precipitated by a history of coughing two weeks previously, which was diagnosed due to a pneumonia infection. Signs of cardiomegaly with widened heart borders, signs of heart failure with increased jugular venous pressure, hepatomegaly, ascites, and peripheral edema. Mitral and tricuspid regurgitation are found. Bilateral mix rhonchi were found on auscultation. Cardiomyopathy in HIV/AIDS

Table 1. Echocardiographic Criteria for the Diagnosis of NVM.[10]

Chin Criteria (1990)	Jernni Criteria (1999)
Absence of any other coexisting cardiac structural abnormality	Absence of any other coexisting cardiac structural abnormality
Numerous, excessively prominent trabeculations and deep intertrabecular recesses	Numerous, excessively prominent trabeculations and deep intertrabecular recesses
Views: parasternal long axis, subxyphoid, and apical	Views: parasternal short axis, and apical
Focus on depth of recesses	Focus on a 2-layer structure
Measured in end-diastole	Measured in end-systole
Ratio of distance from the epicardial surface to the trough of the trabecular recesses and distance from the epicardial surface to peak of fabeculation ≤0.5	Ratio of thick nor compacted layer to thin compacted ≥2 Perfused intertrabecular recesses suplied by intraventricular blood on color Doppler analysis

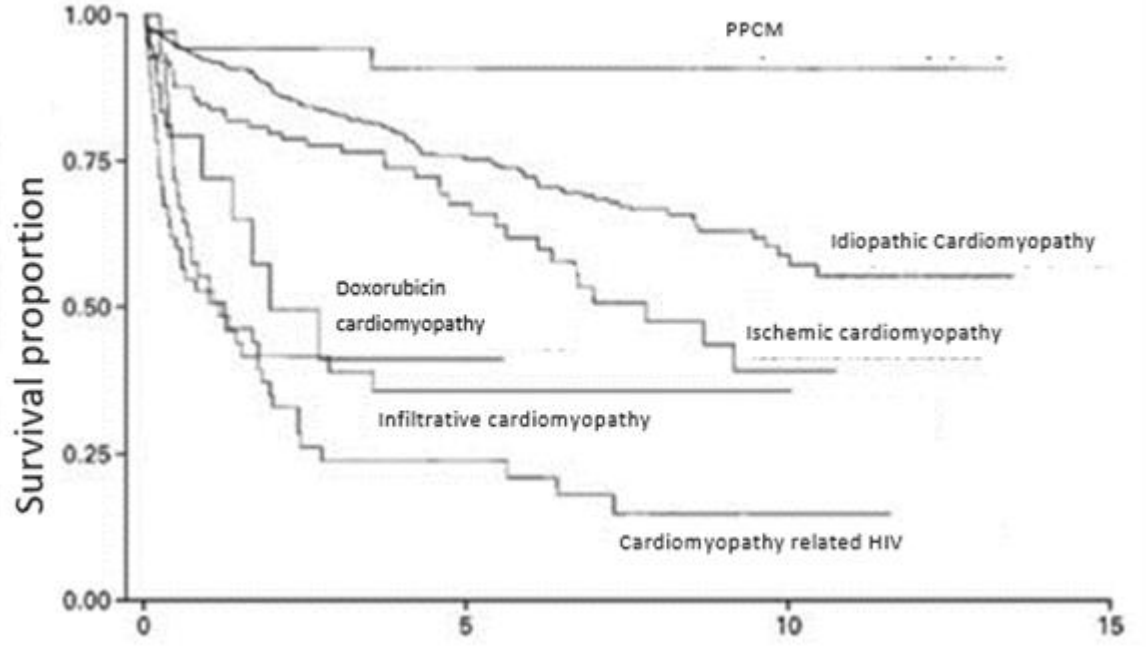

Figure 5. The Kaplan-Meier curve shows the estimation of the survival of cardiomyopathy with various etiologies.[9]

is generally dilated cardiomyopathy characterized by enlargement of one or both ventricles and decreased systolic function.[4] This patient showed cardiomegaly and increased bronchovascular as well as infiltrates on chest x-ray results. Echocardiography helps assess ventricular function and cardiac morphology. Echocardiography should be performed in patients with high cardiovascular risk factors with straightforward cardiovascular complaints. The echocardiography showed all chamber dilatation, global hypokinetic, and a significant decrease in LV systolic function (LVEF 16%). There is also a prominent and deep trabeculation intratrabecular, which we suspect is LVNC. LVNC is a disorder in the developmental phase of the heart caused by myocardial compaction. In the normal process, the myocardium gradually condenses from the epicardium inward and the intertrabecular to the capillaries.[9] Therefore, a screening echocardiogram must be performed in HIV-infected patients, especially if they have cardiovascular risk factors due to the high prevalence of asymptomatic diastolic disorders and systolic dysfunction. According to clinical practice, an echocardiographic evaluation should also be performed in patients with persistent or unexplained pulmonary complaints and in patients with viral infection at baseline and evaluated 4-6 months later.

In general, compared to patients with cardiomyopathy, HIV/AIDS has a worse prognosis than patients with other causes of cardiomyopathy. In a study before the HAART era, patients with AIDS and cardiomyopathy died on average 101 days from AIDS complications, whereas patients without cardiomyopathy had a median survival of 472 days. Several factors are associated with a poorer prognosis. In studies of children with vertical HIV transmission, mortality was higher if left ventricular contractility was compromised or left ventricular dimensions, thickness, mass, wall stress, blood pressure, and pulse were increased. Early onset of heart failure has an excellent prognosis. Bad. More than half of patients die within 12 months of heart failure. Likewise, encephalopathy is a predictor of mortality in patients with cardiomyopathy.[5]

ART is a broad category of treatment regimens usually consisting of three or more antiretroviral drugs expected to reduce the quantity of plasma HIV-l RNA. The cornerstone of ART is the co-administration of different drugs that inhibit viral replication through several mechanisms so that the spread of virus resistant to one agent is inhibited by the action of the other two agents. Six basic kinds of HAART medications focus on various viral lifecycle stages: Nucleoside/Nucleotide Reverse Transcriptase Inhibitors (NRTIs), Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs), Protease inhibitors (PIs), Integrase Strand Transfer Inhibitors (INSTIs), Fusion inhibitors (FIs) and Chemokine Receptor Antagonists (CCR5 Antagonists). Zidovudine, a reverse nucleoside transcriptase inhibitor, inhibits mitochondrial DNA polymerase, causes mitochondrial damage, and leads to focal myocardial necrosis. Treatment with AZT is associated with reversible, dose-dependent damage to skeletal and cardiac myocytes.[11]

Based on the national guidelines for medicine services HIV treatment in Indonesia 2019, first-line ARV therapy in adults, including pregnant women and breastfeeding, consisting of 3 ARV, the alloy must consist of 2 drugs in the NRTI group + 1 drug in the NNRTI group. TDF + 3TC (or FTC) + EFV in fixed-dose combination form is the first line of choice for ARV therapy recommended, with moderate quality of evidence. If TDF + 3TC (or FTC) + EFV is contraindicated or not available,

the options are AZT + 3TC + EFV, AZT + 3TC + NVP, TDF + 3TC(or FTC) + NVP (highly recommended, moderate quality of evidence). TDF + 3TC (or FTC) + EFV can be used as an alternative first-line antiretroviral therapy (recommendations according to condition, moderate quality of evidence).[12]

Treatment

Cardiomyopathy therapy in HIV/AIDS is, in principle, the same as non-ischemic cardiomyopathy therapy. Medical therapy uses diuretics, beta-blockers, aldosterone antagonists, and angiotensin-converting enzyme (ACE) inhibitors.[4] In this patient, during the congestive phase, diuretic therapy was received, namely furosemide 3x20 mg, then the dose was gradually reduced according to the patient's clinical condition. For failure therapy, the patient was given captopril 3x 6.25 with the dose increased gradually, spironolactone 1x 25 mg, and bisoprolol given after the congestive condition was resolved with an initial dose of 1x1.25 mg. The infection became a precipitating factor and was treated immediately; this patient received antibiotic therapy. HIV management in these patients received TLE therapy (Tenofovir, Lamivudine, and Efaviren). After starting medical therapy, serial echocardiography should be performed at 4-month intervals. In patients with clinical deterioration or who do not respond to medical treatment for two weeks, a myocardial biopsy may be considered to look for a potentially treatable cause of cardiomyopathy. If it is possible to evaluate myocyte mitochondria, the NRTI class of ARVs should be stopped if abnormal mitochondria are found.[9]

Intravenous immunoglobulin (IVIG) has been reported to help treat acute cardiomyopathy and nonspecific myocarditis in non-HIV-infected patients. Monthly infusion of immunoglobulin in children with HIV minimizes left ventricular dysfunction and reduces left ventricular peak wall stress. IVIG inhibits the production of cytokines that play a role in myocardial damage, such as TNF alpha and IL−1. In addition, the therapeutic effect of IVIG may be due to the induction of soluble cytokine receptors and the release of IL−1 receptor antagonists.[1] The patient's nutritional status should be thoroughly evaluated, and patients with deficiencies should receive supplementation. Supplementation with selenium, carnitine, multivitamins, or all three may be beneficial, especially in patients with anorexia, wasting syndrome, or diarrhea.

4. Conclusion

Cardiomyopathy in patients with HIV/AIDS is dilated cardiomyopathy, which is acquired due to various etiological factors such as the HIV itself, cytokines, myocarditis, drugs, and malnutrition. Sufferers have a worse prognosis than other cardiomyopathy sufferers, with a relatively short survival. There is no specific therapy for cardiomyopathy in HIV/AIDS. Based on epidemiological studies, the incidence of cardiomyopathy in HIV/AIDS patients has decreased after the widespread use of HAART. Hence, prevention and early treatment of HIV/AIDS is an essential factor in reducing morbidity and mortality due to cardiomyopathy.

5. Declaration

5.1 Ethics Approval and Consent to participate
Patient has provided written informed consent prior to involvement in the study.

5.2. Consent for publication
Not applicable.

5.3 Availibility of data and materials
Data used in our study were presented in the main text.

5.4 Competing interests
Not applicable.

5.5 Funding Source
Not applicable.

5.6 Authors contributions
Idea/concept: ZF. Design: ZF. Control/supervision: HM. Data collection/processing: ZF. Analysis/interpretation: ZF. Literature review: ZF. Writing the article: ZF. Critical review: HM. All authors have critically reviewed and approved the final draft and are possible for the content and similarity index of the manuscript.

5.7 Acknowledgements
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