

# Human Immunodeficiency Virus–Associated Myocarditis

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## Abstract

Alterations in the immune system likely play an important role in the pathogenesis of heart muscle disease in HIV-infected patients. Immune Reconstitution Inflammatory Syndrome is a well-known entity causing myocarditis in HIV-infected patients. To our knowledge, a correlation of direct HIV-associated myocarditis has not been described previously. We report a case of acute myocarditis presenting with complete heart block in a patient with AIDS. The case underscores the importance of recognizing this potential complication of AIDS and calls for renewed vigilance concerning cardiac manifestations of HIV.

## INTRODUCTION

Human immunodeficiency virus (HIV) infection and AIDS have a well-recognized association with myocarditis and dilated cardiomyopathy<sup>1-7</sup>. This increased predisposition is multifactorial and may include the direct effects of HIV itself, co-infection by opportunistic organisms, toxic effects of commonly used medications or illicit drugs, and nutritional deficiencies.<sup>3-5,8</sup> Further, autoimmunity can be an important contributor to the pathogenesis of cardiomyopathy in these patients as many studies demonstrated the presence cardiac-specific antibodies in HIV patients when compared with HIV negative controls.<sup>8,9</sup> Thus, although the precise mechanisms are poorly understood, alterations in the immune system likely play an important role in the pathogenesis of heart muscle disease in HIV-infected patients.

Immune reconstitution inflammatory syndrome (IRIS) is one such example of an alteration in the immune system that is exclusively recognized in the HIV/AIDS population. IRIS is a collection of inflammatory disorders in which clinical deterioration occurs despite recovery of the immune system after highly active antiretroviral therapy (HAART).<sup>10-14</sup>

Numerous manifestations of disease that involve several different organ systems have been described. Despite the growing incidence of IRIS and the increased prevalence of myocarditis and cardiomyopathy in HIV-infected patients, involvement of the cardiovascular system is not recognized as a manifestation of IRIS. There are a few case reports, which describe the myocarditis in AIDS patients immediately after the start of HARRT, but here we describe a patient with AIDS in whom myocarditis developed even

before the start of HARRT. He presented with myocarditis and later he was found to be HIV positive. To our knowledge an association between purely HIV –associated myocarditis has not been described previously.

## REPORT OF CASE

A 31-year-old man with no past medical presented to the emergency department with a 2-day history of light-headedness and palpitations. Associated symptoms included mild dyspnea on exertion, vague abdominal discomfort, nausea, vomiting, diarrhea, and generalized fatigue. He denied fever, chest pain, orthopnea, paroxysmal nocturnal dyspnea, history of syncope, or known previous cardiac disease.

Vital signs recorded at triage were a temperature of 35.2°C, blood pressure of 79/43 mm Hg, and pulse rate of 45 beats/min. Physical examination revealed scleral-icterus, coarse breath sounds bilaterally, mild abdominal distention, and minimal leg edema. Cardiac examination demonstrated a non-displaced point of maximal impulse; a regular rhythm without murmurs, rubs, or gallops; and no jugular venous distention. Laboratory data were obtained (Table 1).

**Figure 1**

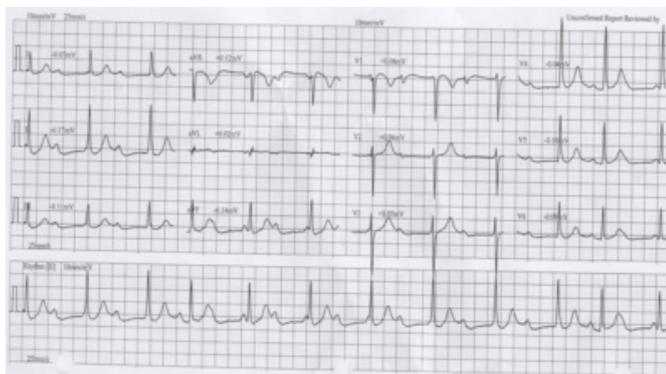
Table 1:

Na	135 mEq/L
K	4.0 mEq/L
BUN	8 mg/dl
Cr	0.9 mg/dl
Blood Glucose	77 mg/dl
ESR	49
Lyme titer	<0.91
CPK	199 ng/ml
CPK MB fraction	0.7 ng/ml
ANA	Negative
Troponin	0.23 ng/ml

High troponin in first set of lab was highly indicative of myocarditis. During initial evaluation, the patient suddenly developed third degree heart block on the monitor but he remained asymptomatic (Figure 1).

**Figure 2**

Fig 1



Subsequent electrocardiography (ECG) showed sinus tachycardia and complete heart block. Transthoracic echocardiography demonstrated a left ventricular ejection fraction of 40% with mild global hypokinesis, moderate mitral regurgitation, and small pericardial effusion. No prior echocardiograms were available for comparison. Chest radiography showed bilateral good air entry. The patient was admitted to the cardiac care unit, where he experienced multiple episodes of complete heart block. Transcutaneous pacemakers were placed to deal with the complete heart block. He was further managed with intravenous fluids and electrolyte replenishment. Work up for the myocarditis was sent which included ESR, Lyme Titer, ANA, serology for parvo, EBV and HIV. Empirical broad-spectrum antibiotics were administered. ESR was elevated. Later, Patient's rapid HIV came out positive, which was confirmed by western blot test. All other test was reported negative including blood culture for staphylococcus and streptococcus. Stool examination was negative for ova and parasites. At this time, diagnosis of HIV-associated myocarditis was made after ruling out other possible causes.

Patient's troponin started trending down in two days and patient's EKG started showing normal sinus rhythm without any blocks. No permanent pace maker was placed and patient was referred for electrophysiological study.

## DISCUSSION

The actual etio-pathogenesis of cardiac injury in HIV infection is not clear. It is however generally agreed that several factors come into play either singly or in combination to produce cardiac pathology<sup>15</sup>. There is a wide range of hypotheses regarding the pathogenesis of HIV associated heart muscle disease. These include myocardial invasion with HIV itself, opportunistic infections, viral infections, and autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, endothelial dysfunction, autonomic dysfunction, and prolonged immunosuppression.

Myocarditis is defined histologically by the Dallas criteria, which require the presence of an inflammatory infiltration of the myocardium with adjacent myocytes necrosis or degeneration that is not typical of the ischemic damage associated with coronary artery disease<sup>16</sup>. However, the use of this strict definition may be inappropriate in the context of an impaired immune response.

Three histological patterns of myocarditis have been described in patients with AIDS:

- Lymphocytic infiltration with myocyte necrosis 17, which meets the Dallas criteria;
- Lymphocytic infiltration without inflammation 18; and
- Myocyte damage without evidence of inflammatory infiltrate 19

The prevalence of myocarditis in HIV infected patients has been difficult to establish with estimates ranging from 6%<sup>20</sup> to 52%<sup>21</sup>. The virus itself may cause myocarditis in HIV infection, either directly or indirectly via autoimmune processes, or via one of many opportunistic organisms<sup>22</sup>. No specific etiologic factor was found in more than 80% of cases of myocarditis in one series<sup>23</sup>. Many organisms have been implicated in the development of myocarditis in HIV infected patients.

The diagnosis of myocarditis requires a high index of suspicion based upon symptoms and/or compatible physical

findings such as fever and signs of heart failure.

Non-specific ECG changes may occur such as sinus tachycardia, conduction defects and repolarization abnormalities<sup>24</sup>, and there may be radiological evidence of cardiac enlargement or pulmonary edema.

Echocardiography offers a practical, non-invasive means of assessing cardiac size and function. The Echo features of myocarditis are non-specific and often identical to those associated with cardiomyopathy. Indeed, differentiation between the two conditions can only be made histologically. Some workers have demonstrated dyskinesia of the left ventricle with or without dilatation or generalized four-chamber enlargement<sup>25</sup>.

Clinical presentation of HIV associated myocarditis in symptomatic patients is generally similar to myocarditis due to other causes. The absence of symptoms and signs of heart disease does not however exclude cardiac involvement, as occurrence of sub-clinical cardiac abnormalities with possible fatal consequences in this population has been described<sup>26</sup>. Diagnosis requires the possibility of cardiac involvement to be borne constantly in mind and suspected if symptoms and/or compatible physical findings emerge. Electrocardiography (ECG) is a useful screening tool in patients with HIV infection, and ECG changes may precede echocardiographic abnormalities. Patients with abnormal ECG patterns should be further investigated.

Echocardiography has been shown to be extremely useful for the diagnosis and monitoring of HIV associated myocardial disease. Computed tomography or magnetic resonance imaging may help but are not widely used for diagnosis. The need for routine myocardial biopsy is controversial and associated risks are significant – sensitivity is low, especially in patchy lesions, and beyond research protocols its use is limited to patients with extensive cardiac damage with no identifiable cause<sup>27</sup>.

Treatment for HIV related myocarditis is generally similar to that for non-HIV related myocarditis. Patients with myocarditis have enhanced sensitivity to digoxin and anticoagulation presents risks to patients with cerebral vasculopathy and possible aneurysm formation. The use of immunosuppressive regimens is controversial and no convincing benefits have been reported other than with intravenous immunoglobulin<sup>28</sup>, whose efficacy may reflect inhibition of cardiac auto antibodies by competition with Fc receptors or dampened effects of cytokines and cellular growth factors.

The introduction of highly active antiretroviral therapy (HAART) regimens has substantially modified the course of HIV disease by lengthening survival and improving quality of life of HIV-infected patients<sup>29</sup>. There is also good evidence that HAART significantly reduces the incidence of cardiovascular manifestations of HIV infection. By preventing opportunistic infections and reducing the incidence of myocarditis, HAART regimens have reduced the prevalence of HIV-associated myocarditis to about 30%<sup>30</sup>. One Italian study reported the prevalence at 1.8%, an almost 7-fold reduction from the pre-HAART era<sup>31</sup>. In that study there is no conclusive evidence that HAART reverses cardiomyopathy, but it does appear that by preventing profound immunosuppression and the development of AIDS, heart muscle remains healthier<sup>31</sup>.

Cardiovascular abnormalities are frequent in HIV infected patients but clinically discrete. Cardiologists and physicians all over the world are reporting more heart muscle disease. With current advances in HIV/AIDS management and increased survival, cardiac manifestations of HIV disease including HIV related myocardial disease will become more important and encountered more frequently. Since cardiac complications are often clinically inapparent, periodic screening of HIV positive patients is recommended, especially in those with low CD4 counts or receiving treatment with cardiotoxic drugs. The heart may be a marker of the HIV infected patient's overall health, and a decline in cardiac function should trigger more comprehensive evaluation. As the role of infection and inflammation in many other cardiovascular diseases is now recognized, identification of the molecular mechanisms of HIV related myocarditis might have broader implications for a wide range of patients.

### References

1. Feldman AM, McNamara D. Myocarditis. *N Engl J Med.* 2000; 343(19): 1388-1398 doi: 10.1056/NEJM200011093431908.
2. Magnani JW, Dec GW. Myocarditis: current trends in diagnosis and treatment. *Circulation.* 2006; 113(6): 876-890. Doi: 10.1161/CIRCULATIONAHA.105.584532.
3. Prendergast BD. HIV and cardiovascular medicine. *Heart.* 2003; 89(7): 793-800. doi:10.1136/heart.89.7.793.
4. Rerkpattanapit P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. *Arch Intern Med.* 2000;160(5):602-608. doi:10.1001/archinte.160.5.602.
5. Klatt EC. Cardiovascular pathology in AIDS. *Adv Cardiol.* 2003;40:23- 48. doi:10.1159/000073174.
6. Barbaro G. Cardiovascular manifestations of HIV infection. *Circulation.* 2002;106(11):1420-1425. doi:10.1161/01.CIR.0000031704.78200.59.
7. Barbarina G, Barbaro G. Incidence of the involvement of

- the cardiovascular system in HIV infection. *AIDS*. 2003;17(suppl 1):S46–S50.
8. Currie PF, Boon NA. Immunopathogenesis of HIV-related heart muscle disease: current perspectives. *AIDS*. 2003;17(suppl 1):S21–S28. doi:10.1097/00002030-200311210-00013.
9. Currie PF, Goldman JH, Caforio AL, et al. Cardiac autoimmunity in HIV related heart muscle disease. *Heart*. 1998;79(6):599–604.
10. Shelburne SA III, Hamill RJ, Rodriguez-Barradas MC, et al. Immune reconstitution inflammatory syndrome: emergence of a unique syndrome during highly active antiretroviral therapy. *Medicine (Baltimore)*. 2002;81(3):213–227. doi:10.1097/00005792-200205000-00005.
11. Shelburne SA, Montes M, Hamill RJ. Immune reconstitution inflammatory syndrome: more answers, more questions. *J Antimicrob Chemother*. 2006 Feb; 57(2): 167–170. Epub 2005 Dec 14. doi:10.1093/jac/dki444.
12. Hirsch HH, Kaufmann G, Sendi P, Battegay M. Immune reconstitution in HIV-infected patients. *Clin Infect Dis*. 2004 Apr 15; 38(8): 1159–1166. Epub 2004 Apr 5. Doi: 10.1086/383034.
13. Battegay M, Nuesch R, Hirschel B, Kaufmann GR. Immunological recovery and antiretroviral therapy in HIV-1 infection. *Lancet Infect Dis*. 2006; 6(5): 280–287. Doi: 10.1016/S1473-3099 (06) 70463-7.
14. Lipman M, Breen R. Immune reconstitution inflammatory syndrome in HIV. *Curr Opin Infect Dis*. 2006; 19(1): 20–25. Doi: 10.1097/01.qco.0000200543.80712.01.
15. Sani MU, Okeahialam BN (2005) Epidemiology and pathogenesis of HIV related heart disease: a review. *Nig J Med* 14: 255–260
16. Aretz HT, Billingham ME, Edwards WD, Factor SM, Fallon JT, Fenoglio JJ Jr, et al (1987) Myocarditis. A histopathologic definition and classification. *Am J Cardiovasc Pathol* 1: 3–14
17. Anderson D, Virmani R, Reilly JM, O' Leary T, Cunnion RE, Robinowitz M, et al (1988) Prevalent myocarditis at necropsy in AIDS. *J Am Coll Cardiol* 11: 729–739
18. Lewis W, Grody WN (1992) AIDS and the heart: review and consideration of pathogenic mechanisms. *Cardiovasc Pathol* 1: 53–64
19. Lafont A, Wolff M, Marche C, Clair B, Regnier B (1987) Overwhelming myocarditis due to *Cryptococcus neoformans* in an AIDS patient. *Lancet* 2: 1146–1146
20. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G (1998) Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS Investigators. *AIDS Res Hum Retroviruses* 14: 1071–1077
21. Levy WS, Simon GL, Rios JC, Ross AM (1989) Prevalence of cardiac abnormalities in human immunodeficiency virus infection. *Am J Cardiol* 63: 86–89
22. Sani MU, Okeahialam BN, Aliyu SH, Enoch DA (2005) Human Immunodeficiency Virus (HIV) related heart disease: a review. *Wien Klin Wochenschr* 117: 73–81
23. Kaul S, Fishbein MC, Siegel RJ (1991) Cardiac manifestations of acquired immune deficiency syndrome: a 1991 update. *Am Heart J* 122: 535–544
24. Sani MU, Okeahialam BN, Ukoli CO (2004) Electrocardiographic abnormalities in Nigerian AIDS patients. *Trop Card* 30: 3–6
25. Levy WS, Vargheese PJ, Anderson DW, Leiboff RH, Orenstein JM, Virmani R, et al (1988) Myocarditis diagnosed by endomyocardial biopsy in HIV infection with cardiac dysfunction. *Am J Cardiol* 62: 658–659
26. Kaminski HJ, Katzman M, Wiest PM, Ellner JJ, Gifford DR, Rackley R, et al (1988) Cardiomyopathy associated with the acquired immune deficiency syndrome. *J Acquir Immune Defic Syndr* 1: 105–110
27. Prendergast BD (2003) HIV and cardiovascular medicine. *Heart* 89: 793–800
28. Lipshultz SE, Orav EJ, Sanders SP, Colan SD (1995) Immunoglobulins and left ventricular structure and function in pediatric HIV infection. *Circulation* 92: 2220–2225
29. Zareba KM, Lipshultz SE (2003) Cardiovascular complications in patients with HIV infection. *Curr Infect Dis Rep* 5: 513–520
30. Barbaro G (2005) reviewing the cardiovascular complications of HIV Infection after the introduction of highly active antiretroviral therapy. *Curr Drug Targets Cardio- vasc Haematol Disord* 5: 337–343
31. Pugliese A, Isnardi D, Saini A, Scarabelli T, Raddino R, Torre D (2000) Impact of highly active antiretroviral therapy in HIV-positive patients with cardiac involvement. *J Infect* 40: 282–284

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