Case reports

Fulminant myocarditis during HIV seroconversion: recovery with temporary left ventricular mechanical assistance

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A 32-year-old male was admitted to our intensive care unit for low cardiac output syndrome. Echocardiography was suggestive of extensive hypokinesia and the ejection fraction was 0.22. Serological tests, including anti-HIV antibodies (ELISA), were negative. The patient was intubated and an intra-aortic balloon pump was inserted. Twenty-four hours after admission a paracorporeal left ventricular assist device (LVAD-MEDOS) was implanted. The left ventricular function showed progressive improvement with normalization of the ejection fraction on day 19. The device was removed on day 20. Before discharge, the patient admitted that he had had unprotected sex with numerous male acquaintances; anti-HIV testing turned positive. The final diagnosis was fulminant myocarditis during HIV seroconversion.

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Case report

A 32-year-old Caucasian male was admitted to our intensive care unit for a low cardiac output syndrome. One week earlier, he had had pharyngitis and myalgias that had resolved spontaneously, and he complained of chest pain and worsening dyspnea lasting 3 days. He was a sculptor. He reported smoking 20 cigarettes per day, and occasional cocaine and hashish use. He denied the use of intravenous drugs. His blood pressure was 90/50 mmHg and his heart rate 130 b/min; peripheral vasoconstriction, bilateral basal crackles and hepatomegaly were present. Laboratory tests showed a white cell count of 14 000/mm^3, a hemoglobin level of 18 g/dl, and a platelet count of 86 000/mm^3; myocardial enzymes were elevated (total creatine phosphokinase 2297 IU/l, MB 398 U/l), as was troponin I (20.6 ng/ml). ECG showed ST-segment elevation in all leads and echocardiography indicated a normal left ventricular size with extensive hypokinesia (ejection fraction 0.22); a moderate pericardial effusion was present.

At admission, several serological tests were done. IgG and IgM for *Mycoplasma pneumoniae, Legionella, Chlamydia trachomatis, Chlamydia psittaci, Borrelia burgdorferi, Treponema pallidum*, Rickettsias, hepatitis C virus, measles and mumps were all negative. Hepatitis B surface and *Aspergillus* antigens were negative. Blood, throat swab, stool and urine cultures were all negative. No significant variations were noted in the titers of antibodies to herpes simplex virus types 1, 2, *Cytomegalovirus*, Varicella zoster virus, Epstein-Barr virus, Coxsackie virus B 1, 2, 3, 4, 5, 6, Echovirus, respiratory syncytial virus, Parvovirus B 19, *Toxoplasma gondii, Chlamydia pneumoniae* and rubella. Anti-HIV antibodies (ELISA) (AXSYM HIV-1/2GO Abbott, Abbott Park, IL, USA) were negative as was immunological testing (antinuclear, antiextractable nuclear antigens, anti-DNA, and rheumatoid factor).

Coronary angiography showed a normal epicardial coronary system. The cardiac index was 1.8 l/min/m^2. The patient's conditions worsened; he was intubated and an intra-aortic balloon pump was inserted. Twenty-four hours after admission a paracorporeal left ventricular assist device (LVAD-MEDOS, Stolberg, Germany) was implanted, utilizing an 80-ml artificial ventricle. At

surgery, the epicardial surface appeared hyperemic with widespread hemorrhagic petechiae. The portion of myocardium removed from the apex for cannulation of the left ventricle was histologically analyzed.

After starting LVAD support, the patient was weaned from cardiopulmonary bypass without complications. The hemodynamic profile rapidly improved, with further progress during the first week after LVAD implantation (Table I). Initially the LVAD was set at a fixed rate of 70 b/min, to give a calculated pump output of 6.3 l/min. Continuous veno-venous hemofiltration was started on the first postoperative day and continued for 5 days because of anuria, associated with a marked creatine phosphokinase increase (peak value 60 059 IU/l, predominant skeletal muscular fraction).

On the 6th post-implant day the patient was extubated. Inotropic support was progressively reduced and stopped on day 16. The renal and liver functions showed only mild transient abnormalities. The left ventricular function, monitored by means of two-dimensional echocardiography, showed progressive improvement, with normalization of the shortening fraction (40%) and of the ejection fraction (0.50) on day 19. Clinical and hemodynamic improvement (Table I) allowed removal of the device on day 20, after a gradual lowering of the pump rate to 40 b/min and of the calculated pump output to 3.8 l/min. No device-related complications were observed during the LVAD support time.

Before discharge, the patient admitted unprotected sexual contacts with multiple unknown men, the last just 4 weeks before hospital admission. For this reason, 32 days after the first negative test, the anti-HIV test (ELISA) was repeated, and was found positive. Anti-HIV western blot analysis (HIV-1 Western Blot 7 Sorin, Milan, Italy) confirmed the seroconversion, since it was positive for p17 (++), p24 (+++), and gp 160 (+) but negative for p31, p41, p51, p55, p66, and gp 120. The serum p24 antigen (VIDAS HIV P24 Bio Merieux, Marcy l'Etoile, France) was also positive (9.1 pg/ml); a serum sample stored on the day of admission was retested for anti-HIV antibodies and confirmed negative, but was positive for a high concentration of the p24 antigen (55.9 pg/ml). The CD4 and CD8 cell counts were respectively 693/mm^3 and 3237/mm^3, and the CD4+/CD8+ ratio was 0.2. The plasma HIV-1 RNA level (HIV b.DNA Bayer, Leverkusen, Germany) was 174 469 copies/ml. The final diagnosis was acute myocarditis during HIV seroconversion.

Biopsy of the ventricular myocardium (1 × 0.8 cm) obtained at the time of LVAD implantation was routinely processed. Multiple 5 μ-thick histological sections were obtained for routine (hematoxylin-eosin) and investigative stains (Masson's trichrome, monoclonal antibodies to CD45, CD3, CD20, CD4, CD8, CD34, myeloperoxidase). Histological examination showed severe interstitial edema and numerous capillary hemorrhages, with extensive cardiomyocyte damage, consisting of diffuse areas of contraction band necrosis. Rare intravascular thrombi were also present. An interstitial inflammatory infiltrate was present, consisting of macrophages, lymphocytes and neutrophil granulocytes (Fig. 1) and was associated with prominent perivascular nuclear basophilic debris. Immunochemical investigation showed relatively sparse lymphocytes with an absolute prevalence of CD3-positive lymphocytes (T lymphocytes) (Fig. 2). Additional immunohistological investigations with antisera for Toxoplasma and *Cytomegalovirus*, and *in situ* hybridization for Epstein-Barr virus (Eber 1, Eber 2 probes) were all negative.

Immunohistochemical evaluation for the presence of HIV antigens was performed using a monoclonal antibody directed against the p24 viral protein (Dako, Milan, Italy)[1]; the polymerase chain reaction (PCR) for HIV *pol* and *gag* genes were performed as previously described[2]; they were both negative.

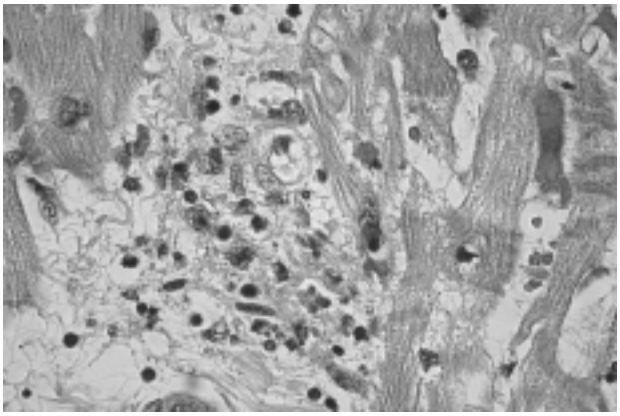

Figure 1. *Histological section of the myocardial biopsy showing an inflammatory interstitial infiltrate mainly composed of mononuclear cells and granulocytes (hematoxylin-eosin 250× original magnification).*

Table I. Hemodynamic profiles: pre-, on- and post-left ventricular assist device (LVAD).

	Pre-LVAD	Early post-implant	1 week post-implant
Mean arterial pressure (mmHg)	75	60	80
Central venous pressure (mmHg)	14	10	11
Mean pulmonary arterial pressure (mmHg)	32	25	20
Pulmonary capillary wedge pressure (mmHg)	25	10	12
Cardiac index (l/min/m^2)	1.8	2.8	3.5

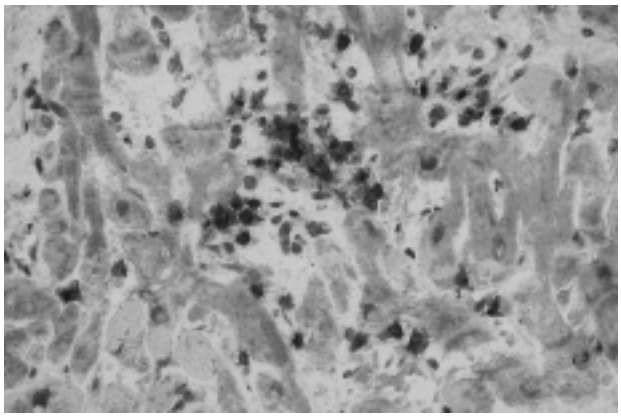

Figure 2. *Numerous CD3-positive lymphocytes (T lymphocytes) may be seen in the inflammatory infiltrate (immunochemical stain, acetaminophen, for CD3; 200× original magnification).*

Twelve months after the diagnosis the patient referred leading an almost normal life without any signs or symptoms of congestive heart failure. His echocardiography was normal. The HIV-1 RNA level was 11 217 copies/ml, the CD4 cell count was 624/mm^3 and the CD4+/CD8+ ratio was 0.36. He is still on enalapril therapy 5 mg daily, started before hospital discharge; no antiretroviral therapy has been started.

Discussion

An acute retroviral syndrome may occur in up to 93% of patients with HIV infection[3]. The most common symptoms are fever, arthromyalgia, adenopathy, pharyngitis, and rash. Only 3 cases of myocarditis associated with possible primary HIV infection have been reported[4-6] but 2 of them lacked a demonstration of the seroconversion, and the clinical and echocardiographic picture were more suggestive of dilated cardiomyopathy than acute myocarditis. In the third case[6], the diagnosis of myopericarditis was based on the presence of aspecific transient electrocardiographic and echocardiographic abnormalities in the context of severe rhabdomyolysis, and no other cardiological investigation was done.

Fulminant myocarditis may have an excellent prognosis if aggressively treated[7]. The proportion of patients who recover and who are weaned from mechanical support ranges from 10 to 70%[8]. The LVAD-MEDOS is one of the devices that has been used successfully to support either the left or both ventricles until recovery. Just as other pulsatile paracorporeal devices, it may be placed easily and its versatility (biventricular assist device, LVAD and right ventricular assist device) is suited to the dual-ventricular features of fulminant myocarditis. No study on HIV patients has been reported so far.

The reported prevalence of cardiac involvement and of myocarditis in patients with HIV infection ranges from 8 to 42%[9,10]. Cardiac manifestations generally became clinically evident late in the course of the disease, mostly in end-stage AIDS patients, when the CD4 count decreases to less than 400/mm^3 [11], and may include pericardial effusion, myocarditis, dilated cardiomyopathy, endocarditis, pulmonary hypertension, malignancies, and drug-related cardiotoxicity[12]. Various opportunistic infections and cardiotropic viruses may be responsible for the cardiac damage which, particularly in the late stages of the disease when the immunosuppression is advanced, is not necessarily directly related to HIV[11,12]. Our case is noteworthy in that fulminant myocarditis occurred during documented seroconversion, when the CD4 count was normal and no opportunistic infections were present.

The pathogenesis of HIV-related cardiomyopathy remains unknown. The cardiac damage in our patient may have been consequent to a direct action of HIV, or to an autoimmune process induced by HIV, or to a toxic effect of locally secreted cytokines such as tumor necrosis factor-alpha[13]. Other cardiotropic viruses cannot be completely ruled out, though in this case laboratory testing excluded the most common causes of infective myocarditis.

Several studies have provided evidence that HIV may infect a small number of cells in the cardiac tissue of some patients, but the detection of HIV did not discriminate between symptomatic and asymptomatic cases[14], was not correlated with histopathologic or clinical evidence of myocarditis[14,15], and in most cases the true cause of the myocarditis remained uncertain. It is difficult to demonstrate HIV in cardiac tissues: immunohistochemistry, culture, southern blot analysis, *in situ* hybridization, and PCR have been used, but HIV was not always detectable, even when myocarditis was documented histologically. At PCR analysis HIV sequences were found in myocytes of 2 of 5 patients with cardiac symptoms and of 6 of 10 without[14], but Bowles et al.[16] failed to detect HIV proviral DNA in the hearts of 32 HIV infected children, suggesting that myocyte HIV infection and viral DNA integration are rare; similarly, *in situ* hybridization indicated the presence of HIV in cardiomyocytes of only 15 to 57% of patients[9,11,15]. Findings were similar in HIV-associated polymyositis[17]. Technical problems apart, cardiomyocytes lack the primary HIV receptor, CD4, and experimental studies did not prove that wild-type HIV-1 can infect these cells[18]. It is possible that *reservoir* cells may activate inflammatory networks and cytokines inducing tissue damage. Thus, in the present case, the failure to demonstrate the presence of HIV does not exclude a relationship between viral infection and pathological and clinical signs of acute myocarditis during HIV seroconversion.

Data in the literature regarding the treatment of acute HIV infection are controversial[19]. Our patient was not given antiretroviral therapy because when the serological diagnosis of HIV was made he had already

considerably improved, and in order to avoid drug-induced cardiotoxicity. To our knowledge, this is the first case of acute fulminant myocarditis reported during documented HIV seroconversion, and the first report of cardiac support with LVAD in an HIV-associated condition; our patient recovered completely from the myocarditis, with no antiretroviral therapy. Screening for recent HIV infection might be included in the evaluation of patients with myocarditis.

References

1. Nebuloni M, Pellegrinelli A, Ferri A, et al. Etiology of microglial nodules in brains of patients with acquired immunodeficiency syndrome. J Neurovirol 2000; 6: 46-50.
2. Rusconi S, De Pasquale MP, Milazzo L, et al. Loss of antiviral effect owing to zidovudine and lamivudine double resistance in HIV-1-infected patients in an ongoing open-label trial. Antivir Ther 1997; 2: 41-8.
3. Schacker T, Collier AC, Hughes J, Shea T, Corey L. Clinical and epidemiologic features of primary HIV infection. Ann Intern Med 1996; 125: 257-64.
4. Fath-Ordoubadi F, Van Der Watt MJ, Noble MI. Early presentation of dilated cardiomyopathy as a part of seroconversion illness in human immunodeficiency virus infection. Clin Cardiol 1997; 20: 738-9.
5. Eerens F, Van Cleemput J, Petermans WE. A probable HIV infection associated with acute non specific myocarditis causing severe dilated cardiomyopathy. Acta Clin Belg 1999; 54: 220-2.
6. Guillaume MP, Van Beers D, Delforge ML, Devriendt J, Cogan E. Primary human immunodeficiency virus infection presenting as myopericarditis and rhabdomyolysis. (letter) Clin Infect Dis 1995; 21: 451-2.
7. McCarthy RE, Boehmer JP, Hruban RH, et al. Long-term outcome of fulminant myocarditis as compared with acute (nonfulminant) myocarditis. N Engl J Med 2000; 342: 690-5.
8. Acker MA. Mechanical circulatory support for patients with acute-fulminant myocarditis. Ann Thorac Surg 2001; 71 (Suppl): S73-S76.
9. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV positive patients. N Engl J Med 1998; 339: 1093-9.
10. Raffanti SP, Chiaramida AJ, Sen P, Wright P, Middleton JR, Chiaramida S. Assessment of cardiac function in patients with the acquired immunodeficiency syndrome. Chest 1988; 93: 592-4.
11. Herskowitz A, Wu TC, Willoughby SB, et al. Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late-stage infection with human immunodeficiency virus. J Am Coll Cardiol 1994; 24: 1025-32.
12. Rerkpattanapipat P, Wongpraparut N, Jacobs LE, Kotler MN. Cardiac manifestations of acquired immunodeficiency syndrome. Arch Intern Med 2000; 160: 602-8.
13. Barbaro G, Di Lorenzo G, Soldini M, et al. Intensity of myocardial expression of inducible nitric oxide synthase influences the clinical course of human immunodeficiency virus-associated cardiomyopathy. Circulation 1999; 100: 933-9.
14. Rodriguez R, Nasim S, Hsia J, et al. Cardiac myocytes and dendritic cells harbor human immunodeficiency virus in infected patients with and without cardiac dysfunction: detection by multiplex, nested, polymerase chain reaction in individually microdissected cells from right ventricular endomyocardial biopsy tissue. Am J Cardiol 1991; 68: 1511-20.
15. Grody WW, Cheng L, Lewis W. Infection of the heart by the human immunodeficiency virus. Am J Cardiol 1990; 66: 203-6.
16. Bowles NE, Kearney DL, Ni J, et al. The detection of viral genomes by polymerase chain reaction in the myocardium of pediatric patients with advanced HIV disease. J Am Coll Cardiol 1999; 34: 857-65.
17. Leon-Monzon M, Lamperth L, Dalakas MC. Search for HIV proviral DNA and amplified sequences in the muscle biopsies of patients with HIV polymyositis. Muscle Nerve 1993; 16: 408-13.
18. Rebolledo M, Krogstad P, Chen F, Shannon KM, Klitzner TS. Infection of human fetal cardiac myocytes by a human immunodeficiency virus-1-derived vector. Circ Res 1998; 83: 738-42.
19. Capiluppi B, Ciuffreda D, Quinzan GP, et al. Four drug-HAART in primary HIV-1 infection: clinical benefits and virologic parameters. J Biol Regul Homeost Agents 2000; 14: 58-62.