HIV-Associated Cardiomyopathy

Etiopathogenesis and Clinical Aspects

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Abstract

Human immunodeficiency virus (HIV) disease is recognized as an important cause of dilated cardiomyopathy. Myocarditis and myocardial infection with HIV-1 are the best-studied causes of cardiomyopathy in HIV disease. HIV-1 virions appear to infect myocardial cells in a patchy distribution with no direct association between the presence of the virus and myocyte dysfunction. Myocardial dendritic cells seem to play a significant pathogenetic role by activating multifunctional cytokines (i.e., tumor necrosis factor-$\alpha$) and the inducible form of nitric oxide synthase that contribute to progressive and late myocardial tissue damage. Coinfection with other viruses (usually, coxsackie-virus B3 and cytomegalovirus) may also play an important etiopathogenetic role.

The introduction of highly active antiretroviral therapy (HAART) has significantly reduced the incidence of myocarditis in HIV-infected patients living in developed countries. By contrast, in developing countries, where the availability of HAART is scanty and greater is the pathogenetic role of nutritional factors, the incidence of HIV-associated myocarditis and cardiomyopathy is increasing with a high mortality rate for congestive heart failure.

A clinical diagnosis of myocarditis or congestive heart failure may be difficult in an HIV-infected patient due to masking of symptoms by concomitant bronchopulmonary disease and/or wasting syndromes, especially in a more advanced stage of HIV disease. Immunomodulatory therapy (intravenous immunoglobulins) may be helpful in adults and children with HIV-associated myocarditis and declining left ventricular function. Data on the role of HAART in the treatment of HIV-associated myocarditis and cardiomyopathy are lacking.

Key Words:

Human immunodeficiency virus · Acquired immunodeficiency syndrome · Cardiomyopathy · Myocarditis · Cytokines · Tumor necrosis factor-$\alpha$
Introduction
Human immunodeficiency virus (HIV) disease is recognized as an important cause of dilated cardiomyopathy, with an estimated annual incidence of 15.9/1,000 before the introduction of highly active antiretroviral therapy (HAART) [1]. The importance of cardiac dysfunction is demonstrated by its effect on survival in acquired immunodeficiency syndrome (AIDS). Median survival to AIDS-related death is 101 days in patients with left ventricular dysfunction and 472 days in patients with a normal heart by echocardiography at a similar infection stage [1]. The unadjusted hazard ratio for death in HIV-related cardiomyopathy compared to idiopathic cardiomyopathy is 4.0; the ratio adjusted after multivariate analysis is 5.86 [1]. The introduction of HAART regimens, by preventing opportunistic infections and reducing the incidence of myocarditis, has reduced the prevalence of HIV-associated cardiomyopathy by about 30% in developed countries [5, 30]. However, the median prevalence of HIV-associated cardiomyopathy is increasing in developing countries (about 32%), where the availability of HAART is scanty and greater is the pathogenetic impact of nutritional factors [27].

Pathologic Features
Pathologic features of AIDS-associated cardiomyopathy are similar to those observed in HIV-uninfected patients. At autopsy, the heart shape is modified, because of ventricular dilation and apical rounding. Heart weight is generally increased, owing to fibrosis and myocyte hypertrophy [2, 15]. On average, long-term survivors have significantly heavier hearts than those dying after a brief disease course. The epicardium is usually normal and coronary arteries do not show significant atherosclerosis. The myocardium is rather flabby and the ventricular wall usually collapses on section [2, 15]. On cut surface, the ventricles show an eccentric hypertrophy, that is, a mass increase with chamber volume enlargement. Although hypertrophy is demonstrated by the increase in cardiac weight, this is not always grossly evident owing to ventricular dilation; the free wall width may be normal, or even thinner than normal, as happens in short-term survivors. Endocardial fibrosis is a common finding, as well as mural thrombi, mainly located at the apex. Dilated cardiomyopathy can be associated with pericardial effusion or infective endocarditis, especially in intravenous drug abusers [2, 15]. On histology, myocytes show variable degrees of hypertrophy and degenerative changes, such as myofibril loss, causing hydropic changes within the myocell. An increase in interstitial and endocardial fibrillar collagen is a constant feature in HIV-associated cardiomyopathy [2, 15].

Etiopathogenesis
Animal Models
Simian immunodeficiency virus (SIV) infection in rhesus macaques is a valuable model in understanding the pathogenesis of cardiac injury associated with retroviral infection in a relevant nonhuman primate model of AIDS [32]. Chronic SIV infection resulted in depressed left ventricular systolic function and an extensive coronary arteriopathy suggestive of injury due to cell-mediated immune response [32]. Two thirds of chronically infected macaques that died of SIV had related myocardial effects. Lymphocytic myocarditis was seen in 9/15 and coronary arteriopathy in 9/15 (six alone and three in combination with myocarditis) upon necropy. In infected macaques, coronary arteriopathy was extensive, with evidence of vessel occlusion and revascularization, and related regions of myocardial necrosis in four macaques. On necropy, two animals had marantic endocarditis and one had a left ventricular mural thrombus. Macaques with cardiac pathology were emaciated to a greater extent than macaques with SIV and similar periods of infection who did not experience cardiac pathology [32].

Myocarditis
Myocarditis is still the best-studied cause of dilated cardiomyopathy in HIV disease. According to the author’s clinical and pathologic experience, HIV-associated myocarditis may be defined as “a process characterized by a lymphocytic infiltrate of the myocardium with necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage associated with coronary artery disease in subjects infected by HIV with or without evidence of opportunistic infective agents” [2]. Myocarditis has been documented at autopsy in 40–52% of patients who died of AIDS before the introduction of HAART [15]. In the Gruppo Italiano per lo Studio Cardiologico dei pazienti affetti da AIDS (GISCA) autopsy series histological diagnosis of myocarditis was made in 30 of 82 patients (37%) with cardiac involvement [2]. Of twelve autopsy patients with dilated cardiomyopathy, ten (83%) had active myocarditis at histological examination of myocardial tissue specimens [2]. Histological findings in HIV-infected patients with myocarditis do not substantially differ