Human immunodeficiency virus (HIV) related heart disease: A review

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Summary. Recent advances in the knowledge of human immunodeficiency virus (HIV) replication and transmission as well as the emergence of effective antiretroviral therapies are leading to longer survival times for HIV-infected individuals. As a result, organ related manifestations of late stage HIV infection, including HIV-related heart diseases have emerged. It is now clear that cardiac involvement in HIV seropositive patients is relatively common and is associated with increased morbidity and mortality.

Cardiac involvement in HIV infection is multifactorial. The epidemiology has changed dramatically since the introduction of highly active antiretroviral therapy (HAART), but studies carried out before the introduction of HAART remain relevant because of limited access to this treatment in many areas of the world. A variety of cardiac lesions have been reported in HIV infection and AIDS, including pericardial disease with effusion and tamponade, nonspecific or infectious myocarditis, dilated cardiomyopathy with global left ventricular dysfunction, endocardial valvular disease due to marantic or infective endocarditis, arrhythmias, pulmonary hypertension and neoplastic invasion. In the post HAART-era, coronary artery disease and dyslipidemia, drug related cardiotoxicity and cardiac autonomic dysfunction are becoming increasingly prevalent. In this review, we highlight the importance of cardiac complications in HIV disease and discuss measures that can be taken to improve survival.

Key words: AIDS, HIV infection, heart disease, antiretroviral therapy, highly active, cardiomyopathy.

Introduction

Cardiac involvement in AIDS was first reported in 1983 by Autran et al. [1] who noted myocardial Kaposi’s sarcoma at autopsy. Since then, there have been several reports recognizing the association between HIV infection and cardiac disease. Cardiovascular complications in the course of human immunodeficiency virus (HIV) infection are multifactorial and may be caused by the virus itself or by opportunistic infections and neoplasms. Highly active antiretroviral therapy (HAART) has prolonged many patients’ lives, but the cardiac sequelae may progress despite HAART. HAART itself is implicated as a cause of lipodystrophy/lipoatrophy, dyslipidemia and insulin resistance that may be associated with an increase in the incidence of cardiovascular disease [2]. The diverse nature of cardiac lesions reported in the literature (Table 1) reflects the various pathologic pathways of cardiac involvement in HIV infection and AIDS [3].

Clinically significant cardiac involvement is not unusual in AIDS, even though the exact prevalence is unknown [4]. Previous reports have described cardiac involvement in 28 to 73 percent of patients with AIDS [4, 5] while other studies based on autopsy findings give a range of 10 to 53 percent [6, 7]. The differences in the reported incidence of heart disease may be accounted for by selection bias (as most published studies are from tertiary referral centers) or due to other confounding factors e.g. intravenous drug use, alcohol and illicit drug use. Both adults and children are affected with severity ranging from incidental microscopic inflammatory findings at autopsy to clinically significant cardiac disease with chronic cardiac dysfunction.

Pericardial disease

The spectrum of pericardial involvement in AIDS ranges from asymptomatic pericardial effusion detected on echocardiography to pericarditis, fatal tamponade and constrictive pericarditis. Dyspnoea is the most frequent presenting complaint when symptomatic [8], whereas acute pericarditis is rare [9]. Pericardial effusion has been reported as the commonest cardiac manifestation of HIV disease [7] with a reported prevalence of up to 38% [10, 11, 12] and an annual incidence of 11% per year in asymptomatic patients in the pre-HAART era [13]. Up to 80% of HIV-related pericardial effusions are small and haemodynamically insignificant and many resolve spontaneously [13]. Large effusions can occur, however, accompanied by either tamponade or evidence of pericardial constriction.
HIV infection should be considered in the differential diagnosis of unexplained pericardial effusion because 33% of cases were HIV associated in one retrospective series [8].

No cause for pericardial disease is found in the majority of patients [2], though many are due to secondary infection or malignant infiltration. Organisms implicated as a cause of pericardial effusion include *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Nocardia asteroides*, *Listeria monocytogenes*, *Rhodococcus equi* and *Chlamydia trachomatis* [8]. *Mycobacterium tuberculosis* and non-tuberculous *Mycobacteria* are also a frequent cause, especially in areas where these are endemic. Other infective causes include *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Toxoplasma gondii*, cytomegalovirus and herpes simplex virus [8]. Malignant infiltrations known to cause pericardial effusion include lymphomas, adenocarcinomas and Kaposi’s sarcoma.

In a recent comprehensive review of the literature, mycobacterial infection was the predominant cause of cardiac tamponade, accounting for 78/176 (44%) of cases, followed by conventional bacterial causes (11%), non-Hodgkin’s lymphoma (8%) and Kaposi’s sarcoma (7%). No identifiable cause was found in 26% of cases [15]. Other causes of pericardial effusions (not restricted to HIV-infected individuals) should be excluded, such as uraemia, cirrhosis and myocardial infarction.

Patients with AIDS who present with an effusion have a lower CD4 (T helper lymphocytes) cell count than those without an effusion [13] and this may account for the increased mortality [16]. The size of the effusion, however, is not associated with prognosis. Echocardiography is the most appropriate diagnostic procedure to detect pericardial effusion and tamponade. Pericardiocentesis can be used for diagnostic purposes and in the treatment of large and symptomatic effusions or tamponade.

### Heart muscle disease

Heart muscle disease is the most important cardiovascular manifestation of HIV infection and is likely to become even more prevalent as HIV infected patients live longer. This may present as myocarditis, dilated cardiomyopathy or isolated left or right ventricular dysfunction [17]. Heart muscle disease is associated with a poor prognosis, and results in symptomatic heart failure in up to 5% of HIV patients [17].

#### Myocarditis

Myocarditis is defined histologically by the Dallas criteria, which require the presence of an inflammatory infiltration of the myocardium with adjacent myocyte necrosis or degeneration that is not typical of the ischaemic damage associated with coronary artery disease [18]. However, the use of this strict definition may be inappropriate in the context of an impaired immune response.

The prevalence of myocarditis in HIV infected patients has been difficult to establish with estimates ranging from 6% [12] to 52% [4]. The virus itself may cause myocarditis in HIV infection, either directly or indirectly via autoimmune processes, or via one of many opportunistic organisms. No specific aetiologic factor was found in more than 80% of cases of myocarditis in one series [19]. Bacterial, viral, fungal and protozoal organisms have all been implicated in the development of myocarditis in HIV infected patients [3, 17, 19]. These include *Cryptococcus neoformans*, *Histoplasma capsulatum*, *Aspergillus fumigatus*, *Candida spp.*, *Coccidioides immitis*, *Toxoplasma gondii*, *Pneumocystis carinii* and microsporidia. Others include *Mycobacterium tuberculosis*, *Mycobacterium avium-intracellulare*, *Staphylococcus aureus*, cytomegalovirus, herpes simplex, Epstein-Barr virus and coxsackie B3 virus.

**Table 1.** Cardiac lesions in AIDS

<table>
<thead>
<tr>
<th>Pericardial disease</th>
<th>Pericarditis</th>
<th>Pericardial effusion</th>
<th>Cardiac tamponade</th>
<th>Constrictive pericarditis</th>
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</thead>
<tbody>
<tr>
<td><strong>Heart muscle disease</strong></td>
<td>Myocarditis</td>
<td>Dilated cardiomyopathy</td>
<td>Isolated left or right ventricular dysfunction</td>
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<tr>
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<td>Non-bacterial thrombotic (marantic) endocarditis</td>
<td>Infective endocarditis</td>
<td>Pulmonary hypertension</td>
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<td>Cardiac malignancies</td>
<td>Kaposi’s sarcoma (KS)</td>
<td>Malignant lymphomas</td>
<td>Cardiac arrhythmias</td>
<td>Vascular lesions</td>
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<tr>
<td>Coronary artery disease</td>
<td>Arteriopathy</td>
<td>Aneurysms</td>
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</table>

**Dilated cardiomyopathy (DCM)**

Cardiac failure due to DCM was first described in 1986 in three patients with AIDS [20]. HIV/AIDS has subsequently become an important aetiologic factor, responsible for up to 10% of cases in the general population [21–23]. A number of cross sectional echocardiographic studies and retrospective post mortem analyses have confirmed the existence of left and biventricular failure in association with AIDS among all the major HIV risk groups [4, 22, 24].

DCM with cardiac dysfunction is associated with a poor prognosis. In one study, the cohort with a normal ejection fraction had a median survival of 472 days compared with a median survival of 101 days among those with poor cardiac parameters [25]. This was independent of CD4 count and stage of HIV disease. Clinical left ventricular dysfunction is rapidly fatal in the later stages of AIDS [26]. Both LV systolic and diastolic function deteriorate as the CD4 lymphocyte count decreases in HIV infection.