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CARDIOLOGY Rounds™

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HIV and the heart

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Introduction

HIV infection is an increasingly important health problem in developed and Third World countries. Cardiac involvement was thought to be rare during the early years of the HIV epidemic. As primary and supportive treatment has improved, and as prevention of opportunistic infections has become more effective, cardiac disease has emerged as an important component of AIDS. Clinically significant cardiac disease occurs in approximately 2.1% to 7.5% of persons infected with HIV.[1-3] Since an estimated 60 – 70 million adults and 10 million children are currently infected with the HIV virus worldwide,[4] the burden of symptomatic cardiac disease is great. In addition, HIV-positive patients as a group can be expected to live longer with the new anti-retroviral therapeutic regimens, especially in developed countries such as Canada. As a result, the prevalence of HIV-related cardiac disease will increase tremendously in this new century.[5]

Unfortunately, the cardiac complications of HIV are often under-recognized and symptoms are often attributed incorrectly to dysfunction in other organ systems. Recognition of the cardiac complications in HIV-infected patients may allow physicians to screen for their onset and apply preventative or therapeutic strategies to reduce morbidity and mortality. The following review will highlight the cardiac sequelae of HIV infection and its treatment.

Pericardial disease

Pericardial disease is the most common cardiac manifestation of HIV infection and can account for greater than 60% of all cardiac lesions identified.[6] The disease spectrum can range from asymptomatic effusions detected on echocardiography to potentially fatal tamponade and constrictive pericardial disease. The cumulative data in HIV-positive adults indicate that approximately 25% have echocardiographically demonstrable pericardial effusions.[7] Most are asymptomatic, small, and without hemodynamic consequence. It is, however, the index presentation of AIDS in Africa where the prevalence of *M. tuberculosis* is increased.[8]

Pericardial disease in HIV-infected patients may be a manifestation of infectious, noninfectious, or neoplastic etiologies. Infectious causes include viruses, bacteria, and fungi. Some previously recognized pathogens are listed in Table 1.

Neoplastic involvement of the pericardium in HIV may also occur. Cardiac lymphoma in HIV patients has been well described and can reflect primary or secondary disease.[9] Most commonly,

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Table 1: Infectious etiologies of pericardial disease in HIV

Virus	Bacterial	Fungal
• CMV	• *S. aureus*	• *C. neoformans*
• HSV	• *K. pneumoniae*	
• Possibly HIV	• *N. asteroides*	
	• *M. tuberculosis*	
	• *M. avium*	

the pericardial involvement is a manifestation of metastasis. Kaposi's sarcoma can involve both the pericardium and epicardium and has a predilection for the epicardium and subepicardial fat.[10] In fact, the first report of cardiac involvement in AIDS was published in 1983 and involved a 24-year-old Haitian woman who was found to have extensive Kaposi's sarcoma involvement of the entire anterior myocardial wall.[11]

Diagnostic pericardiocentesis and/or biopsy is warranted for microbiological and cytological studies when an infectious or malignant etiology is suspected. A diligent attempt must be made to establish a diagnosis under these circumstances since some etiologies (ie, *M. tuberculosis*) are amenable to therapy. Unfortunately, this strategy results in a diagnosis and potential therapy in only 21% of cases.[12] Prognosis is generally poor as pericardial disease frequently occurs in late stage AIDS, and often represents aggressive opportunistic infection or malignancy.[13]

Myocardial disease

Four forms of myocardial disease have been described in HIV-infected individuals (Table 2).

Myocarditis

Many opportunistic infectious pathogens have been identified in cardiac tissue (Table 2). The pathogenesis of cardiac involvement may be secondary to reactivation of latent infections at the myocardial site or, alternatively, a result of a primary infection with a cardiotropic organism.

CMV and Coxsackie virus are examples of cardiotropic viruses previously identified in HIV positive patients with myocarditis.[14,15] Of the cardiotropic viruses, CMV appears to be particularly important. Because CMV is known to cause infection without inflammation, it has been implicated as playing a major role in otherwise idiopathic cases of cardiac dysfunction in AIDS. This is again important therapeutically since a presentation of cardiac dysfunction and disseminated CMV is potentially treatable. In addition, the HIV virus itself may have direct myocardial toxicity or, alternatively, it may mediate a bystander effect.[16] In this regard, HIV in myocardial tissue may promote cell destruction via the immunologic response provoked by its presence in cardiac muscle. A similar mechanism has been proposed for neuroglial cell damage in AIDS-associated subacute encephalitis.[15]

Lymphocytic myocarditis is a histopathological diagnosis in HIV-positive patients in which a mononuclear infiltrate is seen which may or may not be associated with myocardial necrosis. It was noted to be a common finding in early autopsy studies, occurring in approximately 50% of cases.[17,18] The pathological definition contrasts with the definition of myocarditis based upon the Dallas criteria, since the latter requires that an inflammatory infiltrate and myocardial necrosis coexist.

Noninflammatory myocardial necrosis

This too is a well described histopathological pattern in which there is myocardial necrosis in the absence of an inflammatory infiltrate. It has been postulated that the

Table 2: Myocardial diseases in HIV/AIDS
Myocarditis (acute or chronic) • Opportunistic infections (ie, CMV, *M. tuberculosis*, *C. neoformans, T. gondii)* • Lymphocytic myocarditis
Noninflammatory myocardial necrosis
Cardiomyopathy • Dilated cardiomyopathy • Drug-induced cardiomyopathy • Nutritional deficiencies (ie, selenium, thiamine)
Infiltrative neoplasms • Kaposi's sarcoma • Lymphoma

long-term systemic effects of HIV infection may lead to prolonged elevations of endogeneous catecholamine levels which in turn may provoke intermittent microvascular spasm.[19] As a result, focal or widespread myocardial ischemia and necrosis in the absence of an inflammatory infiltrate, may arise. Alternatively, infection by cytomegalovirus (CMV) and other viral agents, including HIV itself, can cause necrosis without inflammation; particularly in the severe immunosuppression of end-stage AIDS.[20,21]

Cardiomyopathy

Dilated cardiomyopathy in HIV-infected patients is associated with a poor prognosis.[22] A recent large, 5 year prospective clinical and echocardiographic study of asymptomatic HIV-positive patients with CD4 counts greater than 400 at inclusion has defined the incidence of dilated cardiomyopathy in this patient population.[23] The mean annual incidence was noted to be 16 cases per 1000 patients. The incidence was higher in those with CD4 counts less than 400.

Current hypotheses[8] concerning the pathogenesis include chronic active myocarditis secondary to HIV infection or coinfection with other cardiotropic viruses. The use of cardiotoxins, including chemotherapeutic agents for the treatment of HIV-related malignancies, nucleoside analogues (ie. AZT) and pentamidine may also be inciting mechanisms. Hypersensitivity reactions in which hypergammaglobulinemia or the development of cardiac autoantibodies and dietary deficiencies (thiamine and selenium) are alternative mechanisms. Importantly, in the previous study,[23] 83% were diagnosed with myocarditis by histology and the majority of those cases were found to have myocardial infiltration with the HIV virus. This supports the hypothesis that a pathogenetic relationship exists between myocarditis and the development of dilated cardiomyopathy and that the HIV virus itself may be an important cardiac pathogen.

Clinicians have assumed that conventional treatment of HIV-related cardiomyopathy and associated congestive heart failure is appropriate. In the absence of randomized clinical data, treatment of these patients should follow the heart failure treatment guidelines proposed by the Agency for Health Care Policy and Research and the American College of Cardiology/American Heart Association Task Force.[24]

Infiltrative neoplasms

Two malignancies, lymphoma and Kaposi's sarcoma, have frequently been described with cardiac involvement in AIDS.[25] Though cardiac involvement with lymphoma remains uncommon, it may be found in up to 20% of autopsy series[26] and should be considered in the evaluation of the HIV patient with cardiac dysfunction. Primary lymphoma of the heart is extremely rare; cardiac involvement usually results from a widely metastatic process.[27] There appear to be three patterns to lymphomatous cardiac involvement. The first is similar to Kaposi's sarcoma with a predilection for the epicardium and pericardium.[28] Presentation as a diffuse infiltrative process[29,30] or endocardial mass[31,32] is also possible. Kaposi's sarcoma is a frequent component of HIV disease and the most common HIV-related malignancy. Although isolated cardiac Kaposi's has been described, cardiac involvement is usually the result of widely disseminated disease.[33] Kaposi's sarcoma in particular appears to have a predilection for the epicardium and pericardium.[33]

It is important to note that therapies for HIV-related malignancies may result in myocardial dysfunction. In this regard, alpha interferon and doxorubicin used in the treatment of Kaposi's sarcoma are known to impair cardiac function.

Endocardial disease

Three forms of endocarditis are recognized in HIV-infected patients. These include marantic (nonbacterial thrombotic), bacterial, and fungal.

- Marantic endocarditis is the most common endocardial lesion associated with HIV infection. It is caused by friable vegetations that consist of platelets within a fibrin mesh with a few chronic inflammatory cells. Left-sided valvular dysfunction is most common and systemic and pulmonary emboli can result in significant end organ damage.
- Bacterial endocarditis may be more virulent in the immunocompromised HIV-infected patient. The most common etiology in intravenous drug users with HIV infection is *S. aureus* (>75%) followed by *S. pneumoniae* and *H. influenzae*. The HACEK group of organisms (Haemophillus spp., *A. actinomycetes*, *C. hominis*, *E. corrodens*, *K. kingae*), previously referred to as culture-negative endocarditis, may also give rise to endocarditis.
- Fungal endocarditis is unusual, however, when it does occur it is usually the result of systemic fungemia. Aspergillus, cryptococcus, and candidal fungal endocarditis have all been reported.[6]

Although endocarditis is a clinical diagnosis, transesophageal echocardiography remains an important tool to detect vegetations and/or ring abscesses and their consequent valvular and myocardial sequelae. The absence of an echocardiographic finding does not preclude the diagnosis and in this case the clinical and microbiological presentation must be considered. Negative cultures in AIDS patients may be the result of prior antibiotic therapy, fungal infection, or fastidious organisms of the HACEK group mentioned previously.

Vascular lesions

Lesions affecting the coronary arteries in HIV-infected patients have been reported. These include fibrocalcific degeneration, vasculitis and perivasculitis. In an anecdotal autopsy series of young HIV-infected adults in which the mean age of death was 27 years, a high prevalence of major eccentric atherosclerotic lesions involving the proximal coronary arteries was noted. It was hypothesized that atherosclerosis may be accelerated in these patients.[34] The pathogenesis of these lesions is not clear.

More recently highly active antiretroviral therapy, which includes two nucleoside reverse transcriptase inhibitors and a protease inhibitor, has been associated with an increased potential risk of coronary atherosclerosis. In one report, 60% of patients prescribed this regimen developed either lipodystrophy, insulin resistance, high cholesterol, or elevated

triglyceride levels.[35] Furthermore, in 10%-20% of these patients, the complications were severe. In order to reduce the burden of atherosclerosis in these patients, aggressive primary prevention will have to be instituted with an agent or agents which can effectively correct the metabolic derangements provoked by antiretroviral therapy.

Cardiac surgery

With the advent of improved anti-retroviral therapy, more HIV-infected patients can be expected to attain an age at which there is a higher prevalence of coronary artery disease requiring aorto-coronary bypass grafting. In addition, as mentioned above, the dyslipidemic syndromes induced by therapy may increase the prevalence of coronary artery disease in this population in particular. However, which HIV-infected patients should be considered for surgery remains poorly characterized.

In one series in which 10 patients were followed for 3 to 46 months, 1 patient died intra-operatively, and 3 patients died of opportunistic infections during follow-up.[36] The remainder were asymptomatic. A follow-up of 40 HIV-infected patients who underwent cardiopulmonary bypass has shown that progression to AIDS is not accelerated[37] by the procedure.

The decision to proceed to surgery remains patient-specific, in consultation with cardiologists, surgeons, and HIV physicians. It requires an estimate of the life expectancy of the patient, the prognosis of the heart disease, its natural history, and the surgical mortality.

Conclusion

Symptomatic cardiac disease related to HIV infection will be a growing public health issue. HIV-infected patients are susceptible to a wide spectrum of cardiovascular abnormalities that pose a diagnostic and therapeutic challenge to clinicians. We, as clinicians, must be diligent in identifying the cardiac sequelae of infection and instituting primary prevention in the those patients who develop diabetes or hyperlipidemia secondary to commonly used anti-retroviral therapy.

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