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Myocardial disease in human immunodeficiency virus (HIV) infection: a review

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HIV und Erkrankungen des Myokards

Zusammenfassung. Die Erkrankung des Herzmuskels ist die wichtigste kardiovaskuläre Manifestation einer HIV Infektion. Mit Zunahme der Lebenserwartung der Patienten wird ihre Prävalenz wahrscheinlich zunehmen. Sie kann sich als Myokarditis, als dilatative Kardiomyopathie, oder als isolierte Dysfunktion des linken oder rechten Ventrikels manifestieren. Die myokardiale Beteiligung bei einer HIV Infektion ist multifaktoriell: Sie kann eine Folge der myokardialen Invasion mit HIV selbst sein, aber auch auf Grund von opportunistischen Infekten, Virusinfektionen, autoimmunen Reaktionen auf eine Virusinfektion, einer medikamentös bedingten Kardiotoxizität, Unterernährung, sowie als Folge der lang andauernden Immunsuppression entstehen. Sowohl Kinder als auch Erwachsene sind betroffen. Der Schweregrad des myokardialen Befalls reicht vom autoptischen Zufallsbefund mikroskopisch sichtbarer myokardialer Entzündung bis zur klinisch wirksamen Herzerkrankung mit chronischer kardialer Funktionsstörung. Die Prognose ist schlecht und resultiert bei 5% aller HIV Patienten im symptomatischen Herzversagen.

Studien aus der Zeit vor der Einführung der hoch aktiven antiretroviralen Therapie (HAART) zeigen eine ungefähr 30%ige Prävalenz einer Kardiomyopathie bei Patienten mit AIDS. Die HAART hat den Verlauf der HIV-Erkrankung deutlich verändert: die Überlebenszeit wurde verlängert und die Lebensqualität der mit HIV infizierten Patienten wurde verbessert. Gute Evidenz deutet darauf hin, dass die HAART auch das Vorkommen der kardiovaskulären Manifestationen einer HIV Infektion signifikant reduziert. Im Vergleich zur „Prä-HAART-Ära" wurde die Prävalenz der HIV assoziierten Kardiomyopathie durch HAART um fast das 7-fache reduziert. Dies wird als Folge der Vermeidung von opportunistischen Infektionen und der Reduktion des Auftretens einer Myokarditis aufgefasst. Die HAART steht allerdings nur einer Minderheit der mit HIV infizierten Individuen zur Verfügung. In den meisten Gebieten der Welt gelten heute noch die in der „Prä-HAART-Ära" erhobenen Prävalenzdaten.

In der vorliegenden Übersicht werden die Ätiologie, die Pathogenese und die Klinik der HIV-assoziierten myokardialen Erkrankung dargestellt und Maßnahmen zur Überlebensverbesserung diskutiert.

Summary. 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. Myocardial involvement in HIV infection is multifactorial and may arise as a result of myocardial invasion with HIV itself, opportunistic infections, viral infections, autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, and prolonged immunosuppression. 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. It is associated with a poor prognosis, and results in symptomatic heart failure in up to 5% of HIV patients.

Clinical pathological studies from the pre-HAART era show a 30% prevalence of cardiomyopathy in patients with AIDS. 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. 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 cardiomyopathy by almost 7-fold from the pre-HAART era. HAART is however only available to a minority of HIV infected individuals in most areas of the world and studies from the pre-HAART period still apply. In this review, the aetiopathogenesis and presentation of HIV related myocardial disease were reviewed and measures taken to improve survival discussed.

Key words: HIV infection, heart muscle disease, HAART, cardiomyopathy.

Introduction

Human Immunodeficiency Virus (HIV) infection is a global public health issue and cardiovascular disease has been well documented in patients with infection [1]. At present, HIV infection is one of the leading causes of acquired cardiovascular disease including heart failure. Highly active antiretroviral therapy (HAART) has prolonged many patients' lives, but the cardiac sequelae may progress despite HAART [2]. 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 [3]. Heart muscle disease results in symptomatic heart failure in up to 5% of HIV patients [3]. 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 [1]. Table 1 shows contemporary classification of cardiomyopathies.

A longitudinal, prospective study of HIV infected infants and children found that left ventricular dysfunction was a significant predictor of overall mortality, even after adjustment for age, height, CD4 cell count, and progressive neurological disease [4]. The first case of rapidly fatal, dilated cardiomyopathy in a patient with AIDS was described in the same study in 1986 [4]. HIV related cardiomyopathy has a poor prognosis, especially in patients with a low CD4 count or coexistent encephalopathy; pathogenesis is multifactorial and treatment options are limited [5].

Clinical and pathological studies from the pre-HAART era show a 30% prevalence of cardiomyopathy in patients with AIDS [6]. In a five-year prospective study with asymptomatic HIV patients, the incidence of dilated cardiomyopathy was 15.9/1,000 [7]. Echocardiographic studies showed early diastolic dysfunction in up to 15% of patients with HIV infection [8, 9]. As cardiomyopathy advances, diffuse hypokinesia, overall dilation of the chambers and systolic dysfunction are observed [10]. Reduced ejection fraction and thicker ventricular walls have been associated with increased mortality, which was found in a multicentre study conducted with children infected by their HIV-positive mothers [4].

The introduction of HAART led to intriguing clinical scenery with a significant change of the clinical manifestations of HIV-associated cardiovascular disease according to the availability of antiretroviral therapy. In the developing countries where HAART is not as yet widespread, myo-pericarditis related to opportunistic infection, dilated cardiomyopathy, myocardial involvement of AIDS-associated tumors dominate the picture. This is in

Table 1. Classification of cardiomyopathies

Primary cardiomyopathies

(a) Genetic
- Hypertrophic cardiomyopathy (HCM)
- Arryhtmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D)
- Left ventricular noncompaction (LVNC)

(b) Mixed (predominantly non genetic)
- Dilated cardiomyopathy (DCM)
- Restrictive cardiomyopathy (non hypertrophied, non dilated)

(c) Acquired
- Inflammatory (myocarditis)
- HIV associated cardiomyopathy (multifactorial)
- Stress provoked ("Takotsubo cardiomyopathy")
- Peripartum cardiomyopathy
- Tachycardia induced cardiomyopathy
- Infants of insulin dependant mothers

Secondary cardiomyopathies

(a)	Infiltrative:	Amyloid, Gaucher's disease, Hurler's disease, Hunter's disease
(b)	Storage disease:	Haemochromatosis, Niemann-Pick disease, Fabry's disease
(c)	Toxicities:	Drugs, Heavy metals, chemical agents
(d)	Endomyocardial:	Endomyocardial fibrosis (EMF), hypereosinophilic syndrome
(e)	Granulomatous:	Sarcoid
(f)	Endocrine:	Diabetes, acromegaly, phaechromocytoma, hypothyroidism, hyperthyroidism
(g)	Cardifacial:	Noonan's syndrome
(h)	Neuromuscular/neurological:	Friedreich's ataxia, Duchenne-Becker muscular dystrophy, tuberous sclerosis, neurofibromatosis, myotonic dystrophy
(i)	Nutritional deficiencies:	Beriberi, pellagra, selenium, carnitine, kwashiorkor
(j)	Autoimmune/collagen:	Systemic lupus erythmatosis, rheumatoid athritis, polyarteritis nodosa, dermatomyositis, scleroderma
(k)	Electrolyte imbalance	
(l)	Consequence of cancer therapy:	Radiation, cyclophosphamide, doxorubicin

contrast to the increase of atherosclerosis-associated cardiovascular disease in developed countries related to HAART-associated lipodystrophy and metabolic syndrome.

Literature search and identification of relevant studies

The relevant English-language articles pertaining to myocardial disease in HIV infection and AIDS were identified by searching the PubMed and EMBASE databases (through June 2007). The following search terms were used to identify primary articles: *Pathogenesis of HIV associated heart disease, HIV and the heart, cardiac manifestations of HIV/AIDS, HIV associated Myocarditis/dilated and drug induced cardiac toxicity in HIV/AIDS*. The references were then manually searched for from the primary articles. Only peer-reviewed reports were included and unpublished data were not searched for. I included prospective and retrospective studies, review articles and case studies.

Aetiopathogenesis

The actual aetiopathogenesis 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 [11]. 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, autoimmune response to viral infection, drug-related cardiac toxicity, nutritional deficiencies, endothelial dysfunction, autonomic dysfunction, and prolonged immunosuppression [12].

Direct HIV myocardial invasion

HIV infection and the myocardial inflammatory process (myocarditis) related to it are the most studied causes of cardiomyopathy in HIV-infected patients [13]. Although it is clear that HIV can affect myocardial interstitial cells, the evidence that the virus can enter cardiac myocytes which do not possess CD_4 receptors is less clear [14]. Possibly, other cells such as the dendritic cells play a role not only as a reservoir, but also as antigen-presenting cells in the context of the major histocompatibility complex and activities of progressive tissue injury mediated by cytokines [15]. HIV was isolated in culture from an endomyocardial biopsy specimen from a patient with AIDS and dilated cardiomyopathy [16]. Using immunocytochemical tests, the HIV-1 antigen has been found in endothelial cells from an endomyocardial biopsy specimen of a patient with left ventricular hypokinesia [17]. HIV-1 virions seem to irregularly infect the myocardial cells, without any direct association between the qualitative presence of the virus and myocyte dysfunction [7]. Necrosis of the myocardial fibers is usually minimal, with associated lymphocytic infiltrates. Additionally the HIV nucleic acid sequences have been reported in the myocardium of HIV infected patients using in-situ hybridization [18]. In that study the distribution of the hybridization assay signal in heart tissue was sparse and did not correlate with any histopathologic or clinical evidence of heart disease. However, HIV sequences might have been contaminants from other cells or from blood since PCR technique is very sensitive [16] and immunohistochemical studies have shown no evidence of group 120 or p24 antigen expression on the heart [19]. It has however been shown through in vitro studies that newly developed human foetal cardiac myocyte cell line could ingest HIV-1 through a specific F_C receptor despite absence of CD_4 receptors on the myocytes [20].

Evidence is accumulating that HIV gp120 may also play an important pathogenic role in HIV cardiomyopathy. A pathogenic role for gp120 in HIV cardiomyopathy is very similar to the role already proposed for gp120 in HIV dementia [21].

The effects appear to involve changes in intracellular ionized free calcium and p38 mitogen activated protein (MAP) kinase activation [22,23] and these have been implicated in myocardial dysfunction [24–26]. The pathogenic role for p38 MAP kinase in myocardial dysfunction has been described both in animal models and in humans [27,28]. A recent study implicated p38 MAP kinase activation in the negative inotropic effect of gp120 in adult rat ventricular myocytes [29]. Similarly, prolonged and repeated activation of p38 MAP kinase in cardiac myocytes by gp120 could result in HIV cardiomyopathy in vulnerable individuals.

Adrenergic signaling is characteristically blunted in humans as well as animal models with myocardial depression, cardiomyopathy, and chronic heart failure from a variety of causes [24, 30]. A physiological role for p38 MAP kinase in adrenergic signaling in cardiac myocytes was recently suggested by an elegant study in a transgenic mice model lacking β_1-adrenergic receptors [31].

Magne et al. [32] provided strong evidence for the regulation of β_2-adrenergic signaling through a MAP kinase/$cPLA_2$ pathway. Human heart failure is associated with a relative decrease in β_1- and an increase in β_2-adrenergic receptors [33]. Thus activation of p38 MAP kinase by HIV gp120 would lead to blunted autonomic responses typical of human cardiomyopathies and chronic heart failure.

The HIV-1 gp 120 has also been shown to damage mitochondria of cardiomyocytes and induce toxicity through induction of cardiomyocyte and endothelial cell apoptosis [34].

The immunohistochemical data from human heart failure patients raise the interesting possibility that CXCR4 is the receptor responsible for the physiological effects of HIV gp120 on adult rat ventricular myocytes. This recently identified binding site has no previously known function in the heart [29]

Controlling the activation and termination of this gp120 signaling pathway in myocytes has considerable potential clinical relevance. The basic mechanisms involved in p38 MAP kinase activation are relevant to chronic heart failure, ischemia, ischemic preconditioning, and adrenergic signaling in cardiac myocytes as well [31]. This gp120 signaling pathway in cardiac myocytes may provide a novel therapeutic target for HIV as well as other cardiomyopathies.

Opportunistic infections

Since HIV infection results in profound suppression of T cell macrophage mediated immunity and since there are significant abnormalities in B cell lymphocytic function leading to abnormalities of humoral immunity, patients with HIV disease frequently face many life threatening infections.

Among patients with myocarditis, opportunistic bacterial, fungal, and protozoan pathogens can be identified in 10 to 15 percent of cases. Many organisms have been implicated in the development of myocarditis in HIV infected patients. Table 2 showed the causes myocarditis in HIV infection.

Cytokines

There is increasing evidence that immune cells especially T lymphocytes are activated to produce cytokines in HIV disease. Reservoir cells (e.g. dendritic cells) may play a pathogenic role in the interaction between HIV and the myocyte and in the activation of multifunctional cytokines (e.g. tumour necrosis factor-alpha [TNF-α], interleukin-1 [IL-1], interleukin-6, interleukin-10) that contribute to progressive late tissue damage and decreased myocardial function [15]. Viral infection in the context of a nonspecific stimulator of monokines such as IL-1 or TNF-α is much more likely to lead to myocarditis and myocyte damage than viral infection alone. TNF-α produces a negative inotropic effect by altering intracellular calcium homoeostasis and possibly by inducing nitric oxide synthesis, which likewise reduces myocyte contractility [15, 47]. Proinflammatory cytokines activate inducible nitric oxide synthase (iNOS), thus stimulating production of NO, a sequence of events that may contribute to the association between dilated cardiomyopathy and encephalopathy in HIV disease [47]. Increased levels of TNF-α and iNOS have been reported in patients with HIV associated dilated cardiomyopathy with iNOS staining intensity correlating with mortality and degree of immunosuppression [15]. The intensity of both TNF-α and inducible nitric oxide synthase staining has been reported much higher in myocardial biopsy samples from patients with HIV-associated cardiomyopathy – specifically in those with a myocardial viral infection independently of antiretroviral treatment – than in those with idiopathic dilated cardiomyopathy [48].

HIV may also inflict damage on myocytes by means of a mechanism of "innocent bystander destruction" proposed for neurological cell damage in AIDS associated sub acute encephalitis [49]. According to this hypothesis, the myocytes are damaged by the toxic enzymes and cytokines released through HIV replication in the interstitium and it may be particularly relevant to the myocardium, since increased numbers of infected interstitial cells have been found in HIV positive subjects with active myocarditis [50].

Table 2. Causes of myocarditis in HIV infection

Bacterial	Mycobacterium tuberculosis [35] Mycobacterium avium-intracellulare [36] Staphylococcus aureus [37]
Viruses	HIV [1] Cytomegalovirus [38] Herpes simplex [39] Coxsakie [40]
Protozoa	Toxoplasma gondii [41] Pneumocystis carinii [42] Microsporidium [43]
Fungi	Cryptococcus neoformans [44] Histoplasma capsulatum [37, 45] Aspergillus fumigatus [46] Candida species [36] Coccidioides immitis [36]

Autonomic dysfunction

HIV infection may be associated with abnormalities of the autonomic nervous system, particularly in advanced disease. Five to seventy – seven percent of patients suffered changes in cardiovascular autonomic reflexes according to the definition of the complication [5]. Cardiovascular autonomic reflexes may be profoundly affected causing postural hypotension, syncope, and cardiorespiratory arrest during invasive procedures [10, 14]. Patients with AIDS are subject to long term physiologic stress due to tragic implications of their disease; the pathway being mediated through prolonged and excessive secretion of catecholamines. This may in turn lead to intermittent microvascular spasm and focal or widespread ischaemia [51], resulting in cardiac damage as seen in some cases of phaeochromocytoma [52]. Autonomic imbalance may also be related to HIV induced neural pathway damage [53] or may be a result of direct beta – receptor stimulation by group 120 protein [54]. These theories are yet to be explored, but they do offer a possible explanation for the presence of non-inflammatory myocardial necrosis associated with AIDS.

Takotsubo cardiomyopathy, a new syndrome, which is characterized by transient left ventricular dysfunction and by a typical left ventriculogram showing transient extensive akinesis of the apical and mid portions of the left ventricle with hypercontraction of the basal segment has been ndescribed in an HIV infected patient [55]. Takotsubo cardiomyopathy seems to be a new type of acute heart failure, which generally has a good prognosis. Myocardial damage by catecholamine overload, adrenoceptor hypersensitivity, and changes of catecholamine dynamics due to stress may cause this condition [56].

Nutritional deficiencies

Nutritional deficiencies are commonly observed in HIV infection, especially in more advanced stages of the disease. They make left ventricular dysfunction more probable [14, 57]. In particular, recent reports have described abnormally low levels of serum selenium in paediatric AIDS patients [58] and in autopsy tissue samples of adult myocardium [59]. A selenium deficiency has been shown to exacerbate the virulence of agents that induce myocarditis [57]. In wasting patients, selenium replacement restores ventricular function and reverts cardiomyopathy [57]. A non obstructive cardiomyopathy associated with selenium deficiency has been described in patients

with advanced HIV disease [60]. The patients improved with selenium repletion [60]. Nutritional factors, especially selenium deficiency, play a significant pathogenetic role especially in developing countries, as reported in a recent study performed in Rwanda. In this study, both by univariate and multivariate analysis, selenium deficiency was independently associated with the development of HIV-associated cardiomyopathy [61]. Malabsorption and diarrhoea promote fluid and electrolyte disorders and nutritional deficiencies [62]. Trace element deficiencies have been directly or indirectly related to cardiomyopathy [62]. Other specific nutritional deficiencies include B group vitamins, folates and zinc and these could worsen immune function or contribute to cardiac dysfunction [63, 64].

Cachexia is common in HIV disease, and wall motion abnormalities and less commonly congestive heart failure have been reported in non HIV infected patients with severe weight loss, anorexia nervosa and starvation [65].

Drugs and toxins

The advent of potent antiretroviral drugs in recent years has had an impressive impact on mortality and disease progression in HIV-infected patients, so that issues related to long-term effects of drugs are of growing importance [66]. Drug-induced cardiotoxicity in HIV-infected patients has been a highly controversial issue, especially due to the association between zidovudine and dilated cardiomyopathy. There is evidence that zidovudine is related to diffuse destruction of ultra structures and inhibition of mitochondrial DNA replication, resulting in lactic acidosis that contributes to myocardial dysfunction [66, 67]. However, no direct clinical relationship has been proved connecting exposure to reverse transcriptase inhibitors and induction of ventricular dysfunction. Interferon alpha, an antineoplastic, antiviral and immunomodulator has been reported to have a variety of reversible cardiotoxic effects including cardiomyopathy and congestive cardiac failure [68].

Doxorubicin, used to treat AIDS-related Kaposi's sarcoma and non-Hodgkin lymphoma, has a dose-related effect on dilated cardiomyopathy [69], as does foscarnet sodium when used to treat cytomegalovirus (CMV) oesophagitis [70]. Amphotericin B used for disseminated fungal infection has also been reported to cause reversible dilated cardiomyopathy [71].

Among HIV-infected patients with cardiac abnormalities, the incidence of alcohol, cocaine and injection drug use is high. An abnormal diastolic function has been demonstrated in patients with substance abuse at various stages of HIV infection and in a control group who were HIV negative [72]. Table 3 showed drugs used in HIV infection and their effect on the myocardium.

Table 3. Medications used in HIV infection and their toxic effects on the Myocardium

Medications	Treatment	Cardiovascular effect
Amphotericin B	Antifungal	Dilated cardiomyopathy, hypertension and bradycardia
Doxorubicin	Kaposi sarcoma	Cardiomyopathy
Foscarnet	CMV	Cardiomyopathy
Ganciclovir	CMV	Ventricular tachycardia
HAART	Antiretroviral	Coronary heart disease
Interferon	Antineoplastic Antiviral Immunomodulator	Myocardial infarction or ischemia cardiomyopathy
Zidovudine	Antiretroviral	Myocarditis and dilated cardiomyopathy

HIV indicates human immunodeficiency virus; *CMV* cytomegalovirus; *HAART* highly active antiretroviral therapy; *CCF* congestive cardiac failure.

Autoimmunity

There is a growing body of evidence to support autoimmunity as the main mechanism causing cardiomyopathy in HIV-infected patients [15, 73]. Compared to patients with idiopathic dilated cardiomyopathy whose inflammatory infiltrates indicate a preponderance of CD4 (+) T cells and B lymphocytes, HIV-infected patients with echocardiographic diagnosis of dilated cardiomyopathy and histopathology compatible with myocarditis present more CD3 (+) and CD8 (+) T cells [14, 73]. The existence of an active immune process within the myocardium was suggested by findings of viral hybridization and increased expression of class I major histocompatibility complex molecules (MHC-I) [74]. As for humoral immunity, myocardial-specific anti-alpha-myosin antibodies were found in 15% of HIV-positive patients, compared to a prevalence of 3.5% in control groups [14, 75]. The HIV gene may provoke cell surface cardiac muscle protein resulting in induction of circulating cardiac auto antibodies which can trigger a progressively destructive autoimmune reaction [76]. Circulating auto antibodies have been identified by means of indirect immunoflourescence in four of six AIDS patients with cardiomyopathy but in none of HIV positive patients without cardiomyopathy [76].

Another finding that supports the theoretical role played by autoimmunity in cardiomyopathy associated with HIV is the therapeutic response of patients with heart failure to immunoglobulins, which act by inhibiting cardiac antibodies, competing with Fc receptors and reducing the secretion and action of inflammatory cytokines.

Endothelial dysfunction

Dysfunction and activation of the vascular endothelium have been described in HIV infection [73]. Circulating markers of endothelial activation such as blood procoagulants and cell adhesion molecules are found less often in these patients. These findings occur because of the secretion of cytokines as a response to the activation of mononuclear cells or to a viral infection in the tunica adventitia or a response to the effects of the viral proteins gp 120 and Tat in the endothelium. Endothelial cells that have been injured and activated can cause tissue damage, inflammation and remodeling, accelerating the develop-

ment of cardiovascular disease. The same mechanism of endothelial dysfunction, changes in leukocyte adhesion and arteritis can stimulate atherogenesis and eventually ischemia and myocardial injury.

HIV-1 has been shown to cause vascular damage. HIV-1 may cause vasculitis and coronary arteritis through activation of cytokines and cell-adhesion molecules and alteration of major-histocompatibility-complex class I molecules on the surface of smooth-muscle cells. Infected cells may also generate reactive oxygen species with the activation of factors that induce apoptosis [77, 78].

Studies have shown that exposure to HAART increased intercellular adhesion molecule-1 (ICAM-1) gene expression and concomitant exposure to TNF-alpha further increased ICAM-1, vascular cell adhesion molecule-1 (VCAM-1), and endothelial-leukocyte adhesion molecule cell surface protein levels [34, 79]. These studies indicate that chronic HAART exposure increases oxidative stress in endothelial cells and induces mononuclear cell recruitment, which may eventually precipitate the cardiovascular diseases observed in HIV-1 positive individuals on antiretroviral therapy [79].

Highly active antiretroviral therapy (HAART) is associated with metabolic and somatic changes that may lead to an increased risk of coronary and cerebrovascular disease. Insulin resistance, impaired glucose tolerance and diabetes mellitus all occur with increased frequency in HIV-seropositive patients receiving protease inhibitors. Impaired glucose tolerance has been found in 16–46% of protease inhibitor recipients and diabetes mellitus in 7–13% [80, 81]. In one study, HAART was independently associated with a 26% relative increase in the rate of myocardial infarction per year of exposure [82].

Myocardial involvement by AIDS-associated tumors

Kaposi sarcoma (KS) affects the myocardium usually as part of a disseminated process.

The tumour plaques are localized to the epicardial space and typically do not involve the underlying myocardium or the overlying parietal pericardium, although concomitant myocardial infiltration with heart failure has been described [83]. The incidence of Kaposi's sarcoma has declined by almost 40% annually since the advent of HAART, and is now less than 10% of the reported incidence in 1994 [84].

Primary lymphomas of the heart occur with increased frequency among patients with AIDS [85]. They are usually of the non-Hodgkin's type and of B-cell origin.

Echocardiography is the most sensitive test for cardiac involvement. Thickened myocardium or luminar tumour masses are found in 50% to 75% of patients. The myocardium may appear speckled with disseminated nodular areas producing heterogenous echogenicity [86].

Types of heart muscle disease in HIV infection

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 [87]. 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 [37], which meets the Dallas criteria;
- Lymphocytic infiltration without inflammation [43]; and
- Myocyte damage without evidence of inflammatory infiltrate [45].

The prevalence of myocarditis in HIV infected patients has been difficult to establish with estimates ranging from 6% [88] to 52% [89]. The virus itself may cause myocarditis in HIV infection, either directly or indirectly via autoimmune processes, or via one of many opportunistic organisms [1]. No specific aetiologic factor was found in more than 80% of cases of myocarditis in one series [39]. Many organisms have been implicated in the development of myocarditis in HIV infected patients (Table 2).

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 repolarisation abnormalities [90], and there may be radiological evidence of cardiac enlargement or pulmonary oedema.

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 [48, 91].

Dilated cardiomyopathy (DCM)

HIV-associated cardiomyopathy has been shown to be associated with more advanced immunosuppression and lower CD4 lymphocyte counts and is independently associated with death [92]. 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 [93]. This was independent of CD4 count and stage of HIV disease. Clinical left ventricular dysfunction is rapidly fatal in the later stages of AIDS [94]. Both LV systolic and diastolic function deteriorate as the CD4 lymphocyte count decreases in HIV infection [1].

Cardiac failure due to DCM was first described in 1986 in three patients with AIDS [95]. HIV/AIDS has subsequently become an important aetiologic factor, responsible for up to 10% of cases in the general population [96–98].

In the developed world, postmortem and echocardiography studies suggest that the prevalence of HIV-associated cardiomyopathy in the pre-HAART era was 30%

to 40% [99]. DCM emerged as the most clinically significant cardiac complication of HIV infection in the western world in the pre-HAART era [95]. In Africa, the home to the majority of the world's HIV infected population, cross-sectional echocardiographic studies of outpatient and inpatient HIV-infected patients suggest a prevalence of cardiomyopathy of 9% to 57% [92]. Although DCM is associated with a significantly reduced CD4 cell count [100], no association has been found between progression of left ventricular dysfunction and the rate of cell count decline [101].

Isolated right ventricular dysfunction

Right ventricular hypertrophy (RVH) has been described as the second most frequent cardiac finding at autopsy of AIDS patient after pericardial effusion [102]. By use of echocardiography, dilatation and dysfunction of the right ventricle have been noted in 4% of HIV positive patients [100]. This may be part of a global myopathic process that leads to biventricular dysfunction and four-chamber dilatation [95], although it can also occur in isolation. RVH may also result from HIV related pulmonary hypertension (HRPH). Pulmonary arterial hypertension (PAH) is a progressive disease of the pulmonary vasculature involving endothelial and vascular smooth muscle cell (VSMC) proliferation, vasoconstriction, right ventricular hypertrophy, and eventually, right heart failure and death. PAH occurs 1000-fold more frequently in HIV patients than in the general population [103]. Although conventional HIV therapy with nucleoside reverse transcriptase inhibitors (NRTIs) leads to regression of PAH, highly active antiretroviral therapy (HAART; two NRTI plus a protease inhibitor) increases the incidence of HIV-associated PAH as much as twofold [104]. Although there are relatively few models for PAH, previous reports indicate that the disease can be initiated by endothelial injury and release of the mitogen endothelin-1 (ET-1). ET-1, in turn, stimulates VSMC proliferation [104]. Tricuspid valve damage from endocarditis is potentially capable of causing right ventricular dilatation as a result of excessive volume load. Right ventricular hypertrophy (RVH) may be evident on the ECG, but echocardiography remains the most useful method of assessing right ventricular function.

Diagnosis of HIV related myocardial disease

Clinical presentation of HIV associated cardiomyopathy in symptomatic patients is generally similar to cardiac disease 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 [105]. 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 [90]. Echocardiography has been shown to be extremely useful for the diagnosis and monitoring of HIV associated myocardial disease [89]. Asymptomatic HIV infected subjects may have abnormal echocardiographic examination, usually with isolated diastolic dysfunction [9, 10]. As the disease progresses systolic dysfunction develops which is initially reversible. In advanced HIV disease, echo findings could be similar to those of idiopathic DCM with dilatation of all heart chambers and evidence systolic dysfunction which is irreversible (Fig. 1). Although early diagnosis of cardiac dysfunction might be beneficial, the cost-effectiveness of routine echocardiographic examination in these patients has not been well established [13]. However, the echocardiogram is well indicated for patients with clinical suspicion or when the CD4 count is below 200 cell/microlitre [7, 10, 14]. 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 [5].

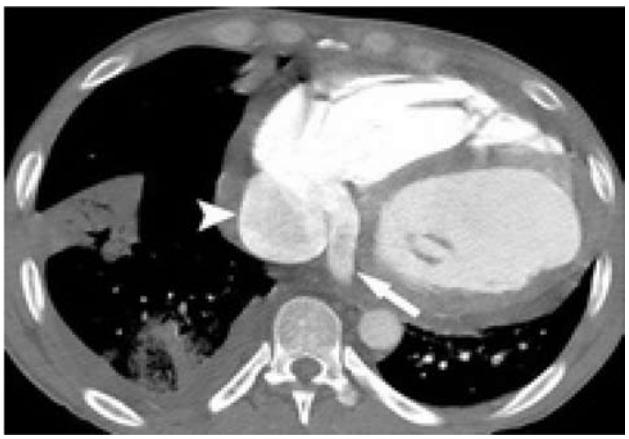

Fig. 1. Contrast-enhanced axial CT scan showing significantly enlarged right and left ventricles and a dilated inferior vena cava (arrowhead) and coronary sinus (arrow), as well as pericardial fluid, right-sided pleural effusion, and parenchymal consolidation in the lower lobe of the right lung

Treatment of HIV related myocardial disease

Treatment for HIV related cardiomyopathy is generally similar to that for non-HIV related, non ischaemic cardiomyopathy. Angiotensin converting enzyme inhibitors and ß blockers are recommended but may be poorly tolerated because of low systemic vascular resistance from diarrhoeal disease, infection or dehydration. 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 [106], whose efficacy may reflect inhibition of cardiac auto antibodies by competition with F_c 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 [107]. 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 cardiomyopathy of about 30% [108]. One Italian study reported the prevalence at 1.8%, an almost 7-fold reduction from the pre-HAART era [109]. 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 [109].

Conclusion

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. HAART is only available to a minority of HIV infected individuals worldwide and studies from the pre-HAART period still apply. In countries where HAART is widely available, physicians should be wary of atherosclerosis-associated cardiovascular disease related to HAART-associated lipodystrophy/metabolic syndrome. Since cardiac complications are often clinically in apparent, 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 recognised, identification of the molecular mechanisms of HIV related heart disease may have broader implications for a wide range of patients.

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