Cardiovascular Pathology in AIDS

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The heart is not the most frequent site for opportunistic infectious or neoplastic processes in patients with AIDS (table 1). However, cardiovascular pathologic findings may occur in up to 40% of AIDS patients at autopsy [2–4]. Cardiac lesions are the immediate cause of death in 1–3% of AIDS patients [5]. The most common significant manifestations of cardiac disease, which can occur at any stage of HIV infection and can lead to death, include cardiomyopathy, dysrhythmias and pericardial effusion with tamponade [6].

Clinical cardiac findings may be present in a fourth to three fourths of adult AIDS patients and may be accompanied by findings that include chest pain, tachycardia, electrocardiographic changes including various arrhythmias, effusions and congestive heart failure. There may be mild cardiomegaly on chest roentgenograms [7]. The prevalence of HIV-related cardiac disease appears to be decreasing with the use of highly active antiretroviral therapy (HAART) [8]. Overall, deaths from cardiovascular diseases in patients dying of AIDS increased slightly from 1987 to 1999, as advances in antiretroviral therapy reduced deaths due to HIV infection after 1995 and the proportion of deaths caused by other conditions increased [9].

Atherosclerosis

Many persons with HIV infection are in the third to fifth decades of life when cardiovascular complications from atherosclerosis are not as frequent as in older persons. Atherosclerotic cardiovascular disease leading to ischemia and myocardial infarction (fig. 1) can and does occur in HIV-infected patients, particularly as the numbers of HIV-infected persons on HAART rise and as the population of long-term survivors from AIDS increases. In one autopsy study, 39% of men and 21% of women dying of AIDS had significant atherosclerosis [4].
Table 1. Opportunistic infections and neoplasms in 565 cases of AIDS at autopsy [1]

<table>
<thead>
<tr>
<th>Disease condition</th>
<th>Number with cardiac involvement</th>
<th>Number with condition diagnosed</th>
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</thead>
<tbody>
<tr>
<td><em>Pneumocystis carinii</em></td>
<td>2</td>
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</tr>
<tr>
<td>Cytomegalovirus</td>
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<td>286</td>
</tr>
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<td><em>Candida</em></td>
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<td>Kaposi’s sarcoma</td>
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<td><em>Mycobacterium avium</em> complex</td>
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<td>104</td>
</tr>
<tr>
<td>Non-Hodgkin’s lymphoma</td>
<td>13</td>
<td>81</td>
</tr>
<tr>
<td><em>Cryptococcus neoformans</em></td>
<td>13</td>
<td>78</td>
</tr>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>5</td>
<td>76</td>
</tr>
<tr>
<td>Toxoplasma gondii</td>
<td>5</td>
<td>51</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>4</td>
<td>13</td>
</tr>
<tr>
<td><em>Coccidioides immitis</em></td>
<td>3</td>
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</table>

Fig. 1. Early infarction with ischemia leads to loss of cross-striations and prominent contraction bands in myocardial fibers seen at high magnification with trichrome staining.

The standard cardiovascular risk factors include the presence of hypertension, hyperlipidemia, diabetes mellitus and visceral fat accumulation, and these are increasingly seen in surviving HIV patients who receive HAART. There are also the nonreversible risk factors including male sex, age greater
than 40 years and family history of coronary artery disease. Other factors include smoking and sedentary lifestyle. In older patients and those with other risk factors, HAART may accentuate these risk factors. It is not clear at this time whether these factors predispose HIV-infected patients to accelerated atherosclerosis [10].

Atherosclerosis arises as a consequence of ongoing endothelial dysfunction and damage that allows the increased uptake of lipids into the intima to stimulate atheroma formation. Over time, the plaque increases in size, with smooth muscle proliferation and overlying thrombus formation as the plaque ruptures. The increasing size of the atheroma narrows the coronary arterial lumen, leading to myocardial ischemia and possible infarction.

HIV infection can produce metabolic disturbances that increase the risk for atherosclerosis. During HIV disease progression, there can be serum lipid abnormalities including decreased LDL cholesterol and increased triglyceride levels [11]. The HIV-associated proteins gp120 and Tat may produce endothelial cell activation in association with cytokines in response to HIV-induced mononuclear cell activation [12]. Coinfection with herpes simplex virus and cytomegalovirus may contribute to vascular endothelial damage [13]. These contributing factors to endothelial alteration may produce endothelial damage that promotes atherosclerosis. Though premature coronary artery disease associated with endothelial dysfunction, hypercoagulability and hypertriglyceridemia were reported prior to the widespread use of antiretroviral therapy including protease inhibitors, the frequency of coronary artery disease and other atherogenic lesions in HIV-infected persons has increased since the advent of HAART with protease inhibitors [14]. These risk factors are associated with the syndrome of protease-inhibitor-associated lipodystrophy (PIAL), and they promote atherogenesis. In this syndrome, there is hypercholesterolemia and hypertriglyceridemia along with insulin resistance and glucose intolerance typical of diabetes mellitus [15]. Glucose intolerance is associated with an increased risk for coronary artery disease. Smoking as an additional risk factor for atherosclerotic heart disease is seen in many of these patients [16]. Peripheral vascular atherosclerosis, however, may not be associated with PIAL [17].

The syndrome of PIAL is characterized by fat accumulation within the abdomen, in the breasts of women and over the cervical vertebrae (‘buffalo hump’), hyperlipidemia and insulin resistance. In addition, there is lipoatrophy involving the face, limbs and upper trunk. These findings are observed in association with protease inhibitors after a median 10 months from initiation of therapy. Diabetes mellitus type 2 is a less common adverse effect. The lipodystrophy syndrome may be a result of the inhibition of cytoplasmic retinoic acid binding protein type 1 and LDL-receptor-related protein involved...
in lipid metabolism that have significant homology to the catalytic site of HIV protease [18].

Increased cholesterol or triglyceride levels may be seen in 50–74% of patients receiving protease inhibitor therapy [18, 19]. The rise in LDL cholesterol is typically small, but triglyceride elevations can be marked, with levels over 1,000 mg/dl, particularly with the use of ritonavir [20]. HIV-infected patients receiving therapy including protease inhibitors have decreased fibrinolysis and increased coagulability, which may be additional risk factors for cardiovascular disease [21].

An increase in thickness of the intima and media of the carotid artery, as measured by B mode ultrasonography, is predictive of an increased risk for myocardial infarction. In one study comparing protease-inhibitor-treated patients with HIV-infected patients who had not received protease inhibitors, and with normal non-HIV-infected controls, half of the patients treated with protease inhibitors had acquired vascular wall lesions. There were slightly significant correlations between carotid lesions and age, male sex and hypercholesterolemia. The most significant correlations occurred between smoking, hypertriglyceridemia and HIV stage. The highest significant correlation occurred with the use of protease inhibitors [17].

Myocardial infarction has been reported in the setting of PIAL, with occurrence from 24 to 29 months following initiation of protease inhibitor therapy [22]. A retrospective study of 4,993 HIV-infected patients treated with different antiretroviral regimens showed that the incidence of myocardial infarction increased in persons over the age of 40 after introduction of HAART [23]. Another retrospective study found a 5-fold increase in the risk for myocardial infarction in patients treated with protease inhibitors [24]. However, another study of ischemic heart disease and HIV infection showed no apparent association with protease inhibitor therapy, but instead an association with more traditional risk factors such as hypertension and hypercholesterolemia [25].

Features of accelerated coronary atherosclerosis have been observed in young persons with HIV infection. These features are intermediate between the coronary arteriopathy of cardiac transplants and typical coronary atherosclerosis. Such features include proximal arterial intimal and medial thickening of an equal degree that was associated with smooth muscle cell proliferation and increased elastic fiber production associated with increased tumor necrosis factor α and interleukin 1α. In two thirds of these cases there was overlying atheroma formation, and in a third of cases mamillated vegetations with intraluminal protrusion were present on the surface of the lesions [26].

However, the chronic debilitated state with cachexia and wasting syndrome brought on by AIDS may lead to regression of atherosclerotic lesions.
AIDS Cardiomyopathy

A congestive (dilated) cardiomyopathy may be identified in both adult and pediatric AIDS patients. By echocardiography, the prevalence of cardiac muscle disease is 15% in HIV-positive patients. Most of these cases are idiopathic, for no specific opportunistic infection or neoplasm can be identified. Patients with symptomatic heart failure from dilated cardiomyopathy, typically present late in the course of AIDS, have low CD4 counts, have myocarditis and have a persistent elevation of antiheart antibodies. Echocardiographic findings include a fractional shortening of <28% with global left ventricular hypokinesia [27]. Even asymptomatic HIV-infected patients may have altered cardiac function. In one study of 61 such patients, all had some degree of left ventricular mass index reduction and diastolic functional abnormalities [28].

It is possible that cardiomyopathy and myocarditis are both immunologic phenomena resulting from HIV-containing lymphocytes in cardiac muscle [7]. Cytokine elaboration by inflammatory cells may contribute as well, since increased levels of both tumor necrosis factor α and inducible nitric oxide synthase have been found in patients with HIV-associated cardiomyopathy [29].

Cardiac myocytes have also been shown to be a direct target for HIV infection, which may result in cardiomyopathy [30]. A proposed autoimmune mechanism for myocardial damage is based upon the observation that autoantibodies to myosin and B-cell receptor can be detected in HIV-infected patients with cardiomyopathy. Abnormal anti-α-myosin autoantibody concentrations have been found to be higher in patients with HIV (19%), particularly those with heart muscle disease (43%), than in HIV-negative controls (3%) [31]. Such autoimmune phenomena may occur when HIV alters myocardial cell surface proteins to elicit an immune reaction. A possible mechanism for an autoimmune contribution to myocardial damage is hypergammaglobulinemia with immune complex formation [7].

In addition, experimental studies with transgenic mice have shown that the HIV protein product of the Tat gene decreases glutathione activity. Glutathione is an important mitochondrial antioxidant. Thus, HIV may induce mitochondrial dysfunction that contributes to myocardial damage and cardiomyopathy [32]. HIV interacts with endothelial cells and inflammatory cells in the heart to upregulate the expression of metalloproteinases [33].

Nutritional status may play a role in the development of HIV-associated cardiomyopathy. Selenium, required for activity of the enzyme glutathione peroxidase, has been reported at lower plasma levels in patients with HIV infection, particularly those with AIDS. Selenium deficiency may be associated with myopathy, cardiomyopathy and immune dysfunction [34].
Cardiac manifestations in pediatric AIDS are similar to those in adults. The most common clinical feature is progressive left ventricular dysfunction, with a prevalence of 5–6% [35]. Mortality is higher when there is decreased left ventricular fractional shortening and an increased size of the left ventricle [36]. In malnourished children, the inverse relationship between cardiac muscle mass and nutritional status suggests that altered metabolic rates with possible increased sympathetic tone account for left ventricular hypertrophy [37].

The gross appearance of the heart with AIDS cardiomyopathy at autopsy is that of a dilated cardiomyopathy with 4-chamber dilation that is more pronounced than hypertrophy, with greater cardiac weight in persons surviving longer. In cases of cardiomyopathy without other specific pathologic findings, the coronary arteries show minimal to no atherosclerosis. The epicardium appears normal. On sectioning, the myocardium is pale and flabby, with minimal to no visible fibrosis. Dilation of the ventricles results in semilunar valvular insufficiency that can be manifested by endocardial fibrosis. In addition, the enlarged cardiac chambers increase the risk for mural thrombosis. Microscopically, AIDS cardiomyopathy resembles other dilated cardiomyopathies, with myocardial fiber hypertrophy, pronounced nuclear enlargement (so-called ‘boxcar’ nuclei) with hyperchromatism and diffuse interstitial fibrosis [38, 39].

**Myocarditis**

AIDS patients with a history of clinical cardiac abnormalities may have a myocarditis, and some cases of AIDS cardiomyopathy may be the result of myocarditis. There is typically 4-chamber dilation. Clinical characteristics of severe symptomatic cardiac dysfunction include a low CD4 count and persistently elevated antiheart antibodies [40]. Involvement of the conduction system by myocarditis may result in first-degree atrioventricular block, left anterior hemiblock and left bundle branch block [41].

Myocarditis is defined as an inflammatory cell infiltrate of the myocardium accompanied by necrosis and/or degeneration of adjacent myocytes not typical of the ischemic damage that is associated with coronary artery disease (fig. 2) [42]. A nonspecific myocarditis composed mainly of lymphocytes often appears in the myocardium of AIDS patients. At autopsy of persons who died from AIDS, myocarditis may be seen in up to half of the cases [7, 43]. Grossly, the heart demonstrates dilation of the cardiac chambers, but, unlike AIDS cardiomyopathy, the heart weight is usually normal and the consistency of the myocardium is not flabby. Microscopically, lymphocytes, along with fewer macrophages, are distributed diffusely as single cells or in small clusters. The lymphocytes are predominantly CD8 cells. Very minimal myocardial fiber...
ischemia or necrosis usually accompanies the myocarditis seen with HIV infection, but the severity of clinical findings may not correlate with the degree of myocardial inflammation and damage [38]. Although septicemia, particularly with bacterial organisms, is not uncommon in patients with AIDS, myocardial abscess formation is rare [1, 44].

Patients with myocarditis may present with fever and infection of the upper respiratory tract or flu-like symptoms for hours to days. Signs and symptoms may occur at rest and include palpitations, atypical chest pain and electrocardiographic alterations including S–T segment elevation followed by T wave inversion in different leads. Laboratory alterations may include elevations of cardiac troponin I, myoglobin or CK-MB mass. An isolated positivity of cardiac troponin I suggests minimal myocardial necrosis (micronecrosis) that may be caused by myocarditis, pericarditis with epicardial extension, autoimmune mechanisms induced by infections or antiviral drugs. An elevated CK-MB

Fig. 2. Myocarditis from HIV infection is characterized by infiltration with scattered small lymphocytes and minimal myocyte necrosis.
and/or cardiac troponin I level with a nondiagnostic electrocardiogram requires clinical skill and echocardiography to differentiate acute myocardial infarction. The frequency of myositis in HIV-infected patients makes myoglobin a less useful marker. Myocarditis may be masked by concomitant bronchopulmonary disease and/or wasting syndromes. A definitive diagnosis of myocarditis may require endomyocardial biopsy [45].

In more than 80% of cases of myocarditis with HIV infection, a specific etiologic factor, such as an opportunistic infectious agent, cannot be identified as the cause of the myocarditis [29]. Nonspecific myocarditis can also appear in persons with a history of intravenous drug use independent of HIV infection, particularly when cocaine use is documented [46].

Since an infectious agent is not often identified in association with myocarditis in AIDS, direct cardiac involvement by HIV may explain some of the cases. In one autopsy study of 440 patients with AIDS, 82 had cardiac findings, with myocarditis seen in 30, and in 29 there was evidence of HIV nucleic acid in myocytes by in situ hybridization. There was a myocarditis present in 25 of those 29 cases, and the inflammatory infiltrate was primarily lymphocytic and composed of CD3 and CD8 cells. HIV may thus cause T lymphocyte activation with cytokine release that potentiates myocardial damage. In 7 of those cases there was coinfection with coxsackievirus group B, in 2 coinfection with Epstein-Barr virus and in 1 cytomegalovirus was found [41]. In HIV-infected children, the two most commonly detected viruses by PCR are adenovirus and cytomegalovirus [47].

HIV may cause direct damage to myocytes and may produce an autoimmune process that secondarily involves the myocardium. Alternatively, HIV may act in concert with other viruses to produce a myocarditis. By in situ hybridization, both HIV and cytomegalovirus can be detected in myocytes of AIDS patients with lymphocytic myocarditis and severe left ventricular dysfunction [30, 41].

The detection of antimyosin antibodies in patients with AIDS and cardiomyopathy suggests an immune process. In addition, the HIV regulatory protein nef binds to major histocompatibility complex class II receptors on antigen-presenting cells, stimulating T lymphocytes to release cytokines such as tumor necrosis factor α, γ-interferon and interleukin 2 that mediate the immune response [29]. Tumor necrosis factor α can produce a negative inotropic effect by altering intracellular calcium homeostasis, mediated by nitric oxide [48]. Both tumor necrosis factor α and nitric oxide synthase can be detected with greater intensity of staining in the myocardium of patients with HIV-associated cardiomyopathy, particularly those with myocardial viral infection [49].

The most common opportunistic infectious agent associated with myocarditis in AIDS is Toxoplasma gondii, observed as often as 12% in one autopsy series with deaths from AIDS between 1987 and 1991 (fig. 3). There may be regional differences in the incidence of T. gondii myocarditis, perhaps
because the natural reservoir of organisms persists more easily in humid environments. Elevation of creatine kinase may commonly occur with myocardial toxoplasmosis. *T. gondii* organisms can produce a gross pattern of patchy irregular white infiltrates in myocardium similar to non-Hodgkin lymphoma (NHL). Microscopically, the myocardium shows scattered mixed inflammatory cell infiltrates with polymorphonuclear leukocytes, macrophages and lymphocytes. *T. gondii* can produce quite variable inflammation along with myocardial fiber necrosis. The three microscopic patterns of involvement by *T. gondii* include acute diffuse myocarditis, focal myocarditis and presence of organisms without significant inflammation or necrosis. In most cases of *Toxoplasma* myocarditis, a *Toxoplasma* encephalitis is also present [1, 50].

In *Toxoplasma* myocarditis, true *T. gondii* extracellular cysts or pseudocysts within myocardial fibers, both of which contain the small 2-μm-sized bradyzoites, are often hard to find, even if inflammation is extensive. Immunohistochemical

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*Fig. 3.* *Toxoplasma* myocarditis has foci of mixed inflammatory infiltrates. Pseudocysts with bradyzoites (inset) are diagnostic but not numerous.
staining may reveal free tachyzoites, the organisms that are found outside of cysts. Otherwise, it is difficult with routine hematoxylin and eosin staining to distinguish these free tachyzoites from fragments of inflammatory cells or myocytes that have undergone necrosis within the areas of inflammation [51].

Fungal opportunistic infections of the heart occur infrequently. They are often incidental findings at autopsy, and cardiac involvement is probably the result of widespread dissemination, as exemplified by Candida and by the fungi Cryptococcus neoformans, Coccidioides immitis or Histoplasma capsulatum. Fungal lesions are characterized grossly by the appearance of multiple small rounded white plaques. They may have a hemorrhagic border, particularly lesions caused by Aspergillus that can be angioinvasive. Microscopically, fungal lesions have variable inflammatory infiltrates and necrosis, and a specific diagnosis is made by identifying yeast forms or hyphae of specific organisms, aided by standard histologic stains such as Gomori methenamine silver or periodic acid-Schiff [38]. The near absence of an inflammatory infiltrate accompanying fungal organisms is a manifestation of immune system failure with progression of AIDS to a late stage when opportunistic infections are more likely to be widely disseminated to organs such as the heart.

Viral causes for myocarditis seen with AIDS include coxsackievirus B3, Epstein-Barr virus and cytomegalovirus [29]. Patients living in endemic areas for Trypanosoma cruzi, a form causing trypanosomiasis, may rarely develop a pronounced myocarditis [52, 53]. Mycobacterium avium complex infection can be widely disseminated and involve the heart with microscopic lesions characterized by clusters of large macrophages filled with numerous acid-fast rod-shaped organisms. Cardiac opportunistic infectious lesions in pediatric AIDS cases are not frequent [36].

Pneumocystis carinii can involve the heart in cases with widespread dissemination of this organism. Grossly, the epicardium and cut surfaces of the myocardium may have a sandpaper-like quality due to the presence of multiple pinpoint foci of calcification. Microscopically, this calcification is not accompanied by significant inflammatory cell infiltrates, but there may be deposits of amorphous granular pink exudate similar to that seen in alveoli with Pneumocystis pneumonia. The cysts may be difficult to recognize, even with the Gomori methenamine silver stain, and diagnosis is aided by immunohistochemical staining [1, 54].

Endocarditis

Both infectious and noninfectious endocarditis may complicate the course of HIV infection. The noninfectious form of endocarditis seen with AIDS is
nonbacterial thrombotic endocarditis (NBTE), also known as ‘marantic’ endocarditis. The debilitation of patients with AIDS, particularly in the terminal course, may predispose to the formation of NBTE. This was once the most common form of endocarditis with AIDS, seen in about 3–5% of persons dying of AIDS at autopsy, most of them older than 50 years. Marantic endocarditis has not been reported in the literature in the era of improved antiretroviral therapy [45].

The lesions of NBTE may involve any valve but are most common on the mitral and aortic valves. The vegetations usually appear grossly as friable pale pink excrescences on the edge of the involved valve and are typically smaller than 0.5 cm (fig. 4). There can be multiple lesions on one valve or lesions on more than one valve. Microscopically, these bland vegetations are composed of platelets and fibrin, sometimes admixed with a few entrapped inflammatory cells. The friable nature of these vegetations predisposes to systemic or pulmonary embolization. Infarcts in the spleen, kidney or cerebrum may result from systemic embolization [7]. A significant number of reported cerebral infarcts seen in patients with AIDS were the result of such embolic phenomena [55]. However, deaths from NBTE with AIDS have not been reported in the HAART era [41].

Infectious endocarditis with HIV infection is most often seen in persons with a history of injection drug use. Persons with a history of injection drug use who are infected with HIV have an increased risk for infective endocarditis

Fig. 4. NBTE appears as small, friable vegetations on the closure margin of the aortic valve cusps.
compared to HIV-seronegative injection drug users. Over 90% of cases of infective endocarditis with HIV infection occur in injection drug users. The mortality rate among HIV-infected patients is higher in those with CD4 cell counts below 200/μl [56]. Infectious endocarditis, particularly in intravenous drug users, can be associated with dilated cardiomyopathy [30, 57]. A case of infectious endocarditis has been reported in an infant with HIV infection [58].

Right-sided endocarditis is more common in persons with HIV infection, because of the preponderance of cases associated with injection drug use, and the tricuspid valve is the most commonly affected valve, in just over half of the cases. Left-sided valvular disease occurs in 45% of cases, and multiple valves are involved in 18%. The presence of left-sided heart involvement is associated with an increased risk of death, compared with right-sided heart involvement [56].

Echocardiography may demonstrate mobile echodense masses attached to the inflow side of valvular leaflets or mural endocardium. Transthoracic echocardiography is useful for detecting relatively large valvular masses. However, perivalvular abscess, leafllet perforation or rupture of valvular chordae are better assessed by transesophageal echocardiography [45].

The vegetations of infectious endocarditis are grossly large, soft and friable, and red to tan in color. The infection often produces valve leaflet destruction, and there can be extension of infection to the adjacent endocardium or myocardium. Microscopically there are numerous neutrophils admixed with bacterial colonies, platelets and fibrin in the vegetations. These vegetations, being friable, often produce septic emboli.

Vegetations that form on the tricuspid valve, or less frequently the pulmonic valve, may predispose to pulmonary embolism and septic pulmonary infarction. Such infarcts may appear as multiple opacities on a chest X-ray. Systemic emboli from left-sided valvular endocarditis often involve the coronary arteries, spleen, bowel, extremities and central nervous system. Cardiac rhythm alterations such as atrioventricular block may suggest the presence of an abscess in proximity to the atrioventricular node. Peripheral pulses may be absent with embolic occlusion, or a pulsating mass may suggest a mycotic aneurysm. Cerebral arterial mycotic aneurysms may lead to intracranial hemorrhage [45].

The most frequent agents isolated in cases of infectious endocarditis seen with HIV infection are *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Haemophilus influenzae* [41]. Other bacterial agents may include *Streptococcus*, viridans group and *Salmonella* species. Salmonellosis typically occurs with non-S.-typhi species, is seen with CD4 counts below 100/μl and has a mortality rate of 50% [59]. *S. aureus* is by far the most common organism (60% of cases). The mortality rate is higher with left-sided valvular disease, multiple valve involvement and with lower CD4 counts. Most patients have a coexisting pneumonia or meningitis [7, 60]. Increasing frequency of resistant
bacterial strains, such as *S. pneumoniae* and *H. influenzae*, puts HIV-infected patients at an increased risk for recurrent endocarditis, particularly when vaccines for these organisms may not be as effective as in immunocompetent patients [61, 62].

Fungal endocarditis may occur with HIV infection. *Aspergillus* species, *Candida albicans*, *Pseudallescheria boydii*, *C. neoformans* and *H. capsulatum* infections have been reported. HIV disease produces immunologic impairment that may predispose patients to fungal infection, including defects in granulocyte numbers and function, defective macrophage phagocytosis and dysregulation of cytokine production. The vegetations of *Aspergillus* endocarditis tend to be large and friable, with possible embolization. *Aspergillus* is difficult to isolate with blood cultures. Microscopically, the vegetations are composed in large part of long branching septate hyphae [61, 63, 64].

**Pericarditis and Pericardial Effusions**

Pericardial effusions, most of which are small and clinically insignificant, may be seen in up to 41% of persons during the course of HIV infection. The incidence is 11% per year for those with AIDS [65]. However, in a third of HIV-infected persons who have such an effusion, it is moderate to severe [66]. In almost half of the cases with a moderate to severe effusion, there is right atrial diastolic compression, and a third of these have evidence of cardiac tamponade requiring pericardiocentesis [67].

Clinical manifestations of pericarditis may include fever, chest pain with radiation of dull pain to the left shoulder (aggravated by supine posture and often decreased by sitting up and leaning forward) and pericardial friction rub (over the left sternal border, usually accentuated by sitting up and leaning forward). Pericardial effusion is suggested by the absence or weakness of the apical impulse with an apparent increase in the area of dullness to percussion over the left chest and over the hepatocardiac angle, muffled heart sounds, a diffuse low-voltage electrocardiogram, electrical alternans of QRS complexes and increased cardiac opacity on chest X-ray [45].

Despite the frequency of effusions, acute pericarditis is uncommon. The characteristic findings of an elevated jugular venous pulse and pulsus paradoxus may be masked by dehydration, with ‘low-pressure tamponade’ [67]. Histologically, mononuclear cells may also be seen as a mild epicarditis, which may account for some pericardial effusions [7]. Tuberculous pericarditis, typically appearing with disseminated tuberculosis, may produce a granulomatous inflammatory reaction, and resultant constrictive pericarditis has been reported with HIV infection [68, 69].
A specific etiology for a pericardial effusion in HIV-infected patients, which can include a variety of infectious agents, is found in about a fourth of cases. When cardiac tamponade is present with AIDS, causes include mycobacterial infection in 20% of cases, bacterial infection (most commonly \textit{S. aureus} or \textit{S. pneumoniae}) in 19%, lymphoma in 7%, Kaposi’s sarcoma (KS) in 5%, viral infection in 3% and fungal infection in 1%, while 45% are idiopathic [70].

Persons with AIDS who have a pericardial effusion, regardless of size, tend to have lower CD4 counts and decreased survival, compared to those without effusions. Pericardial effusions can be seen in the late stages of AIDS where such effusions are occasionally the immediate cause of death. Regardless of etiology, a large pericardial effusion in AIDS carries a high mortality, and treatment with a pericardial window is unlikely to prolong survival significantly [7]. In children with HIV infection, pericardial effusions may be seen in 16–26% of cases. However, the effusions are typically small and asymptomatic [36].

Pathologic findings within the epicardium or pericardium are subtle. Grossly, there may be no apparent changes or minimal opacification of the epicardial or pericardial surfaces. A fibrinous exudate or fibrous adhesions are uncommon. In one study of 52 hearts at autopsy from persons dying with AIDS, there were 38 with a lymphocytic pericarditis, 1 with fibrinous pericarditis and 1 with pericardial fibrosis [71]. Hemorrhagic pericarditis is uncommon and development of constrictive pericarditis unlikely [7].

**Cardiac Neoplasms in AIDS**

A high-grade NHL is one of the most common AIDS-diagnostic diseases seen in the heart, occurring in about one sixth of AIDS cases when lymphoma is diagnosed at autopsy (table 1). Such NHLs with AIDS tend to be seen late in the course of HIV infection when CD4 counts are low. NHLs with AIDS are typically extranodal and widely disseminated. Clinical findings may be nonspecific, and the diagnosis goes undetected, or findings may be related to heart failure and include dyspnea, chest pain and arrhythmias. Sudden death and myocardial rupture have been reported but are rare complications [72]. The serum creatine kinase is unlikely to be elevated. Diagnosis is typically made by echocardiography, with histologic confirmation by endomyocardial biopsy [73].

Grossly, NHLs may produce a patchy pattern of infiltration with white streaks or distinct nodules (fig. 5, 6). Despite the often widespread infiltration by malignant lymphoma, cardiac enlargement and failure are uncommon. Microscopically, the lymphomatous infiltrates extend in and around myocardial fibers, onto the endocardium and over the epicardium. There is little myocardial fiber necrosis or inflammation resulting from such infiltration (fig. 7).
Microscopically, most NHLs seen with AIDS fall into two broad categories, both of B-cell origin. About 30% are high-grade B-cell lymphoma (small non-cleaved) Burkitt-like lymphomas (in the REAL classification), called intermediate grade and classified as small noncleaved-cell lymphomas (Burkitt or Burkitt-like lymphomas) in the working formulation classification, and called Burkitt's lymphoma with or without plasmablastic differentiation (in the Kiel classification). They may also be called AIDS-related Burkitt's lymphomas. These NHLs consist of cells having round nuclei with 1 or more prominent nucleoli and scant cytoplasm. The cells comprise diffuse sheets that form a discrete mass or irregularly intersect and infiltrate normal tissues without significant necrosis. Within the sheets of lymphomatous cells, uniformly distributed

Fig. 5. High-grade NHL appears as pale tan nodules scattered over the epicardial surface.
Fig. 6. High-grade NHL is seen on the endocardial surface as small pale tan nodules.

Fig. 7. Microscopic finding of high-grade NHL showing lymphomatous infiltrates extending in and around myocardial fibers along with little myocardial fiber necrosis.
macrophages containing phagocytosed debris are present, and occasional mitoses are seen. Plasmablastic features including eccentric nuclei and a well-defined Golgi zone may occur [74].

The second broad category of NHLs with AIDS, comprising virtually all primary CNS lymphomas seen with AIDS and about 70% of systemic lymphomas in AIDS, is composed of large cells that are best described as diffuse large B-cell lymphoma (in the REAL classification), which can be either large-cell immunoblastic lymphomas in the working formulation classification (immunoblastic with or without plasmacytic differentiation in the Kiel classification) or large non-cleaved-cell lymphomas in the working formulation classification (centroblastic diffuse in the Kiel classification). The immunoblastic types consist of cells having moderate to large amounts of cytoplasm with or without plasmacytic features of eccentric nuclei and basophilic cytoplasm, large round to oval nuclei and prominent single nucleoli. The large-cell types have less cytoplasm and 1 or more peripheral nucleoli in a nucleus with finely dispersed chromatin. Necrosis is often a prominent feature, and mitoses are frequent [74].

NHLs of the T-cell phenotype are much less frequent in AIDS but can involve the heart [75].

Another type of lymphoproliferative disease seen with HIV infection occurs in association with concomitant human herpesvirus 8 infection and is manifested as a primary effusion lymphoma involving body cavities, including the pericardial sac. In such cases, an effusion is present in which the neoplastic cells can be identified, but a grossly apparent mass lesion is not identified, and only a fibrinous exudate or fibrous thickening of the cavity surface is noted. Microscopically, the mesothelial lining is obliterated and the lymphoma cells have plasmablastic features with medium-sized to large peripherally placed nuclei, prominent nucleoli, basophilic cytoplasm, numerous mitoses, apoptosis and more than 1 nucleus per cell. The cells mark with CD45 and CD138, but are variably positive for CD20. Subserosal lymphatics may contain the neoplastic cells [76].

KS, despite its vascular nature, is not often seen in the heart (table 1). When KS does involve the heart, there is usually widespread visceral organ involvement, and pulmonary involvement will probably be of greater significance [1]. Cardiac involvement by KS is often limited to small subepicardial deposits within adipose tissue which usually do not produce clinically apparent problems. Grossly, the lesions appear red to dark red or purple. Small nodules may coalesce to larger masses. Microscopically, KS is characterized by atypical large spindle to fusiform cells that line slit-like vascular spaces (fig. 8). Red blood cell extravasation, hemosiderin pigmentation and hyaline globules usually accompany the spindle cell proliferation. The lesions have irregular, infiltrating margins. Sometimes the vascular spaces are dilated and sometimes sheets of KS spindle
cells have inapparent vascularity. KS has a propensity to infiltrate around large vascular structures, near epithelial or mesothelial surfaces or near the capsules of organs [77].

Endocardial papillary fibroelastoma has been reported in association with HIV infection. It can produce embolic phenomena similar to vegetations of endocarditis [78]. Atrial myxoma has been reported in a patient with HIV infection [79].

**Drug Toxicity**

Antiretroviral therapy may be associated with cardiac muscle toxicity in adults treated for HIV infection. Zidovudine and other nucleoside reverse transcriptase inhibitors can cause mitochondrial dysfunction as a consequence of the inhibition of mitochondrial DNA polymerase $\gamma$. The mitochondrial dysfunction
may lead to cardiomyopathy [80]. However, a similar cardiac disease in children has not been seen [81]. In addition, the zidovudine-induced mitochondrial disorder with massive liver steatosis, myopathy, lactic acidosis and mitochondrial DNA depletion which affects liver and skeletal muscle does not appear to affect the myocardium [82].

A number of pharmacologic agents may induce significant cardiac arrhythmias. One of the most common of these arrhythmias is prolongation of the Q–T interval, which is thought to develop from myocardial ion channel blockage. Such drugs include macrolide antibiotics such as erythromycin (less frequently clarithromycin), trimethoprim-sulfamethoxazole, fluoroquinolones, amphotericin B, azole antifungals such as ketoconazole, pentamidine, antihistamines, antipsychotic medications such as haloperidol and tricyclic antidepressants [19].

Bradycardia is seen in children treated with amphotericin B. Doxorubicin used in therapies for KS and NHLs has a dose-related effect on cardiomyopathy [83]. α-Interferon administered as part of prolonged antiretroviral therapy or the antivirals ganciclovir and foscarnet may also lead to a dilated cardiomyopathy [84]. Since α-interferon is not associated with myocardial dysfunction in patients without HIV, it may have a synergistic effect with HIV infection [85].

Although it has not as yet been demonstrated that cocaine use by an HIV-infected patient increases the risk of cardiac complications, both cocaine and HIV infection are associated with myocarditis, and cocaine is associated with contraction band necrosis that may accentuate ischemic heart disease and cardiac dysfunction. A hyperadrenergic state with catecholamine release produced by cocaine use may exacerbate myocarditis [86].

**Pulmonary Hypertension**

HIV-related pulmonary hypertension was first described in 1987 and has been observed with increased frequency in association with HIV infection and AIDS [87]. It is a form of pulmonary hypertension in patients for whom no factor other than HIV infection is present to explain the findings. The incidence is estimated to be 1/200 in persons with HIV infection, compared with 1/200,000 in the general population [29]. There is a slight male preponderance and a wide age range, with a median age of 33 years [88]. There does not appear to be an association with either CD4 lymphocyte counts or with the existence of pulmonary infections and the onset of pulmonary hypertension [87].

Clinical findings with HIV-related pulmonary hypertension are similar to primary pulmonary hypertension and include progressive shortness of breath, pedal edema, nonproductive cough, fatigue, syncope and chest pain.
Chest X-ray findings include cardiomegaly and pulmonary arterial prominence. By electrocardiography there is typically right ventricular hypertrophy, right atrial abnormality and right axis deviation. An echocardiogram is likely to demonstrate right heart chamber enlargement, tricuspid regurgitation and paradoxical septal motion [87]. The mean time to diagnosis from onset of symptoms ranges from 6 to 30 months. The mean time from diagnosis to death is 6 months, with death occurring from right-sided heart failure, cardiogenic shock and sudden death. The acute response to epoprostenol therapy is similar to that for non-HIV-infected patients. The course is slightly more fulminant than in patients with primary pulmonary hypertension, with half of the patients dying in a year [88, 89].

There has been no direct evidence for HIV itself in lung tissue as a cause for pulmonary hypertension, either by electron microscopy or immunohistochemical staining. Inflammation resulting from HIV infection, with release of inflammatory mediators and growth factors, such as vascular endothelial growth factor or platelet-derived growth factor, has been postulated as an inciting event. The HIV-1 envelope glycoprotein known as gp120 can stimulate production of endothelin 1 and tumor necrosis factor α with an effect on vascular endothelium [90]. HIV-infected persons who possess the HLA-DR6 and -DR52 alleles have a predisposition to the development of pulmonary hypertension [89]. Regression of HIV-related pulmonary hypertension has been reported in association with successful HAART therapy and suppression of HIV-1 in plasma [91].

Pathologic findings with HIV-related pulmonary hypertension are similar to primary pulmonary hypertension. Histologically, the patterns of disease range from plexogenic pulmonary angiopathy (sometimes in association with lymphoplasmacytic pulmonary infiltrates) to thrombotic pulmonary arteriopathy and to pulmonary veno-occlusive disease [88, 89]. The most common finding is a pulmonary plexiform arteriopathy. Other arterial findings may include isolated medial hypertrophy or medial hypertrophy with intimal fibrosis. Less frequently observed is pulmonary veno-occlusive disease [87].

**Miscellaneous Findings**

Rheumatic inflammatory changes, ranging from rare scattered Anitschkov myocytes to well-formed Aschoff nodules similar to those seen in rheumatic heart disease, are rarely reported to occur in AIDS. However, chronic rheumatic sequelae of fibrosis or valvular disease have not been seen in AIDS [92].

Vasculitis involving small and medium-sized arteries has been infrequently seen in patients with HIV infection. In about a third of cases, the pattern of
vasculitis resembles a distinct type of vasculitis such as polyarteritis nodosa, Henoch-Schönlein purpura or drug-induced hypersensitivity vasculitis. In the remaining patients, the vasculitis has variable features. Such vasculitides may result from HIV-induced immunologic abnormalities, infections and drugs [93, 94].

A vasculopathy involving large arteries including the aorta and its branches has also been described in young adults with AIDS. The features of this vasculopathy overlap with Takayasu’s disease, characterized by involvement of the aorta and its branches by a panarteritis that leads to focal stenosis or occlusive lesions. Grossly there is arterial wall thickening and focal raised intimal plaques. Microscopically, early lesions have infiltrates of neutrophils, macrophages, lymphocytes and occasional Langhans giant cells. Late lesions are marked by fibrosis, intimal thickening and secondary atherosclerotic changes. With large-artery vasculopathy there is a propensity for the appearance of single or multiple aneurysms of variable size. There can be angiogenesis with proliferation of slit-like channels in the adventitia. The appearance of these lesions in the aorta may also be due to vasculitis of vasa vasora or small adventitial arteries in aortic branches. There does not seem to be an association of this vasculopathy with opportunistic infections [94, 95].

Kawasaki disease, also known as mucocutaneous lymph node syndrome, is an acute systemic vasculitis seen most commonly in children aged <5 years. Untreated Kawasaki disease has a mortality rate of 0.8% due to coronary artery aneurysm formation and occlusion during the early convalescent phase of the illness. A similar disease has been described in HIV-infected adults manifesting with fever >5 days’ duration, bulbar conjunctivitis without exudates, swelling and pain in the hands and feet, a diffuse erythematous rash and either an aseptic pharyngitis or tender cervical adenopathy [96].

Aortic root dilation, both progressive and nonprogressive, has been described in HIV-infected children. This dilation has been shown to correlate with increased plasma HIV-1 RNA levels and decreased CD4 counts, as well as left ventricular dilation. Markers of stress-modulated growth, including heart rate, systolic blood pressure, stroke volume or hematocrit, do not correlate with this dilation [97].

Congenital heart disease has been reported in children with HIV infection. Rates of congenital heart disease with HIV infection, however, are not different from those for similarly screened populations. The reported malformations include atrial septal defect, ventricular septal defect, patent ductus arteriosus, tricuspid valve prolapse, mitral valve prolapse, valvar pulmonic stenosis, subaortic stenosis and single coronary artery [98]. By fetal ultrasound, there is increased right and left ventricular wall thickness in the hearts of fetuses of HIV-infected women [99].
References


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