HIV Disease and an Atherosclerotic Ascending Aortic Aneurysm

Humair Mirza, MD, Parag Patel, MD, Krishnamurthy Suresh, MD, Irvin Krukenkamp, MD, William E. Lawson, MD, FACC

State University of New York at Stony Brook, Stony Brook, NY

Cardiovascular dysfunction appears to be an important complication of human immunodeficiency virus (HIV) infection and is being reported with greater frequency. There have been recent reports in the literature of HIV patients who suffer from vascular lesions such as large artery vasculopathy secondary to vasculitis, as well as accelerated atherosclerosis of the coronary arteries. The latter has been linked to patients on protease inhibitors that are used as part of a highly active antiretroviral therapy (HAART) regimen and have also been implicated in a lipodystrophy syndrome. We report a rare case of an HIV-infected patient on HAART who presented with a large ascending aortic aneurysm associated with symptomatic severe aortic regurgitation. A noteworthy finding on pathological analysis of the aorta was an etiology of accelerated atherosclerosis rather than the more expected vasculitis.

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Infection with the human immunodeficiency virus (HIV) is an increasingly important cause of heart disease and symptomatic heart failure. The recent onset of the acquired immunodeficiency syndrome (AIDS) epidemic and its natural history of a short, virulent course leaves most clinicians unfamiliar with the cardiac manifestations of the disease. Cardiac complications tend to occur late in the course of the disease and are becoming more prevalent in our socie-

ty as therapy and survival with HIV improves. Approximately 34.3 million people will be living with HIV infection by the end of mid-2000s, as estimated by The Joint United Nations Program on HIV/AIDS.[1]

If symptomatic heart failure develops in 8%–10% of patients over a 2- to 5-year period, then 3 million new cases of HIV-related heart failure would be expected annually. This number continues to increase.[2] The range of cardiovascular disease in HIV patients includes disease directly due to HIV infection, such as dilated cardiomyopathy (with an estimated annual incidence of 15.9 in 1000 asymptomatic HIV-infected persons),[3] myocarditis and nonbacterial thrombotic (marantic) endocarditis,[4] pericardial effusion,[5] metastatic cardiac malignancies such as Kaposi's sarcoma and non-Hodgkin's lymphoma,[6] and pulmonary hypertension.[2] Disease due to HIV-related treatment is also quite prevalent. Doxorubin, used to treat Kaposi's sarcoma and non-Hodgkin's lymphoma, as well as foscarnet, for cytomegalovirus esophagitis, are known to cause dilated cardiomyopathy.[2] Cardiac arrhythmias have also been described with the use of amphotericin B, ganciclovir, trimethoprim-sulfamethoxazole, and pentamadine.[2]

Vascular lesions, in particular, have become more evident in HIV-infected patients and have extended the spectrum of indicator diseases in HIV infection well beyond the classic opportunistic infections and Kaposi's sarcoma. Joshi and colleagues[7] reported the occurrence of arteriopathy in small and medium-sized arteries in children with HIV, and 2 types of lesions were described. These include inflammatory lesions of vasculitis and perivasculitis in the myocardium and fibrocalcific lesions consisting of intimal fibrosis with fragmentation of elastic tissues, as well as fibrosis and calcification of the media with luminal narrowing. Large artery vasculopathy[8,9] and aortic root aneurysms[10] have also been described with greater frequency as a result of improved treatment and longer survival. The key histological feature in such arteries has been vasculitis, specifically, leukocytoclastic vasculitis of the vasa vasora and periadventitial vessels.[8]

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In addition to vasculitis, accelerated atherosclerosis has been observed in HIV-infected individuals without traditional coronary risk factors.[11-13] Significant coronary lesions, for example, were discovered in 8 HIV-positive subjects aged 23 to 32 years who died unexpectedly.[12] Counterbalancing their profound beneficial impact on the treatment of HIV infection, protease inhibitors have been implicated in a lipodystrophy syndrome. This syndrome includes alterations in lipid metabolism causing marked hyperlipidemia, in particular severe hypertriglyceridemia and increased LDL, as well as insulin resistance, glucose intolerance, fat redistribution, and premature atherosclerotic disease.[14-16] In 1 study, protease inhibitors increased lipoprotein(a) levels by 48% in patients with elevated pretreatment levels.[15] Furthermore, a recent study reported that the 10-year coronary heart disease risk of 91 HIV-infected patients with fat redistribution, estimated using the Framingham risk equation, was significantly elevated when compared with control subjects enrolled in the Framingham Offspring Study.[17] Endothelial dysfunction has also been recently described in protease inhibitor recipients.[18]

We describe in this report a rare case of an HIV-positive patient with an aortic aneurysm secondary to an atherosclerotic process. This is unlike prior reports that have implicated a vasculitic process as the primary etiology.

History

The patient is a 38-year-old male with a history of idiopathic thrombocytopenic purpura (ITP), who has been HIV-positive since 1983, with a CD4 count of 192 cells/mm^3 in July 2001. Normal CD4 counts in adults range from 500 cells/mm^3 to 1500 cells/mm^3. The Centers for Disease Control and Prevention consider HIV-infected patients with CD4 counts of less than 200 cells/mm^3 to have AIDS. The patient had been on highly active antiretroviral therapy (HAART) since 1997 and had a history of oral thrush and oral hairy leukoplakia. He presented with a 4–6 month history of progressive malaise culminating in a 1–2 week history of dyspnea on minimal exertion, orthopnea, and paroxysmal nocturnal dyspnea. Also of note were complaints of fatigue, a nonproductive cough, and nocturia. Upon review of symptoms, he denied chest pain, pedal edema, fevers, or chills. His past surgical history was significant for drainage of a left breast abscess 18 years earlier. He had no drug allergies and was taking trimethoprim-sulfamethoxa-

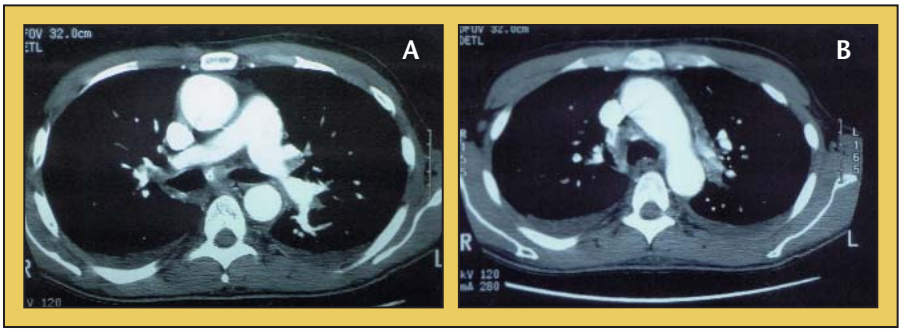


Figure 1. *CT scan of chest revealing an ascending aortic aneurysm* **(A)** *originating above the aortic valve and* **(B)** *involving the aortic arch.*

zole for prophylactic purposes at the time of admission. He had a 10 pack/year history of cigarette smoking and denied any history of alcohol and intravenous drug use or blood transfusions. He also denied any family history of premature coronary artery disease.

Examination and Initial Laboratory Data

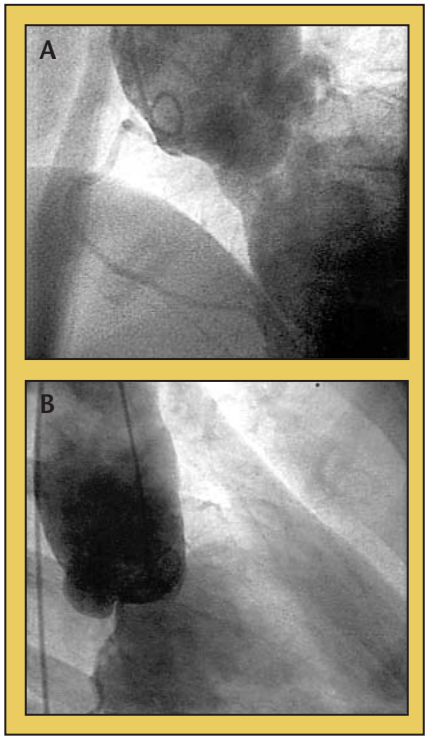
On physical examination, the patient was afebrile with a blood pressure of 129/54 mm Hg, a regular pulse of 85 beats/min, and a respiratory rate of 14/min. Oral examination revealed signs of mucosal thrush. There was no evidence of jugular venous distension, hepatojugular reflux, or bruits. His lungs were normal on percussion and clear to auscultation. Cardiovascular examination revealed a III/VI decrescendo diastolic murmur heard along the right upper sternal border and a III/VI holosystolic murmur at the apex radiating to the axilla. Abdominal examination was benign without evidence of organomegaly, and there was no evidence of cyanosis, clubbing, or edema of his extremities. Electrocardiogram demonstrated left ventricular hypertrophy with strain pattern. Laboratory results revealed mild leukopenia (white blood cell count = 3.4 k/mL, with normal range for the laboratory being 5 k–11 k/mL), 2 sets of negative blood cultures, negative tests (rapid plasma reagin and fluorescent treponemal antibody absorption) for syphilis, and an HIV viral load of 140,000 copies/mL. Viral load in HIV-infected patients of 200 copies/mL to 500 copies/ mL is considered low. Viral load of over 20,000 copies/mL is considered high. A high viral load indicates that the virus is reproducing and the disease will likely progress faster if not treated aggressively. A lipid panel was not performed on this admission. It is common practice in evaluation of young patients with no previous cardiac history to overlook lipid profiles. Lipid profile performed after discharge showed a total cholesterol of 218 mg/dL, LDL cholesterol of 162 mg/dL, and HDL cholesterol of 36 mg/dL.

Hospital Course

The patient was admitted to the cardiac department and started on hydralazine, furosemide, captopril, and metoprolol, as well as lamivudine/zidovudine (Combivir®, GlaxoSmithKline, Research Triangle Park, NC) and lopinavir/ritonavir (Kaletra,™ Abbott Laboratories, North Chicago, IL) as recommended by the infectious disease consultants. He subsequently underwent an echocardiogram and computed tomography (CT) scan. The salient features of his echocardiogram were mild left ventricular (LV) dilatation with mildly to moderately reduced global LV systolic function, moderate LV hypertrophy, as well as aneurysmal dilatation of the aortic root and proximal ascending aorta measuring 4.1 cm and 4.8 cm in diameter, respectively. Aortic annular dilatation was present with severe central aortic regurgitation. In addition, there was moderate mitral and trace tricuspid regurgitation. His CT scan of both chest and abdomen revealed an ascending aortic aneurysm measuring 4.8 cm in dimension originating above the aortic valve and extending to just below the brachiocephalic branch vessels (Figure 1). There was no aneurysmal disease noted in the descending thoracic or abdominal aorta.

Further diagnostic tests included a cardiac catheterization demonstrat-

Figure 2. *Aortogram revealing a dilated aortic root and 4+ aortic insufficiency in the* **(A)** *left anterior oblique and* **(B)** *right anterior oblique views.*



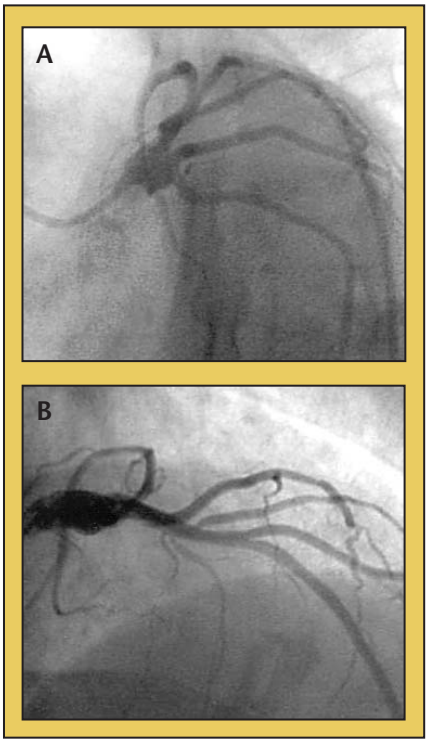


Figure 3. *Coronary angiogram using a 6 French Judkins Left 4 catheter revealing an ectatic and aneurysmal left main coronary in the* **(A)** *left anterior oblique caudal and* **(B)** *right anterior oblique cranial views.*

ing normal right heart and pulmonary pressures, a pulmonary capillary wedge pressure of 15 mm Hg, and a preserved cardiac index. His ejection fraction was estimated at 35% and mild mitral regurgitation was present. Aortography revealed a dilated aortic root and severe aortic regurgitation (Figure 2). Coronary angiography showed a markedly ectatic left main coronary artery measuring approximately 10 mm in diameter (Figure 3). The rest of the coronary vessels had nonobstructive disease. As a result of the above findings, the patient was referred to cardiac surgery for aortic aneurysm repair. No other imaging studies were performed.

In surgery, the anterior surface of the aorta was opened in a longitudinal fashion. Upon inspection, there was evidence of marked annular dilatation (Figure 4) with severe aortic valvular insufficiency. The ascending aorta was noted to be atherosclerotic with endoluminal debris (Figure 5). The ascending aorta was resected and subcommisural plication sutures were placed in the aortic valve. The annulus was re-suspended, and the valve was rendered competent. A felt strip was placed around the aortic annulus using a running prolene suture, which reduced the size of the annulus to approximately 30 mm. A 32-mm Hemashield graft was then sutured into position (Figure 6). Saline infusion testing revealed a competent aortic valve. The distal anastomosis was constructed by making a felt strip sandwich in the distal aorta that was run with a prolene suture. A postoperative transesophageal echocardiogram revealed good coaptation of the aortic valve leaflets.

Pathological specimens were obtained from the ascending aorta. These demonstrated a mild-to-moderate plasma cell infiltrate consistent with severe atherosclerosis without evidence of dissection. The conclusion of the pathologist was that the fundamental alteration was atherosclerosis, not an aortitis. The patient had an unremarkable postoperative course.

Discussion

It can clearly be seen that HIV infection has protean manifestations. With techniques allowing for enhanced detection and early, aggressive treatment producing prolonged longevity in this population, vascular pathology has become an increasingly important manifestation of HIV disease. Prior studies of aortic aneurysms in HIV patients have drawn attention to a strong association between aortic aneurysms and a vasculitic etiology,[8] as well as a syphilitic, tubercular, or other bacterial etiology.[9] To our knowledge, this is the first report of an aortic aneurysm in an HIV-positive patient with atherosclerosis as the likely etiology. It is noteworthy that no angiographic coronary artery stenosis was present in this patient. The localized disease process in this patient is even more likely to be atherosclerotic rather than secondary to vasculitis or dysmetabolic syndromes that more commonly manifest as diffuse disease.

Patients with HIV infection on HAART should be screened for

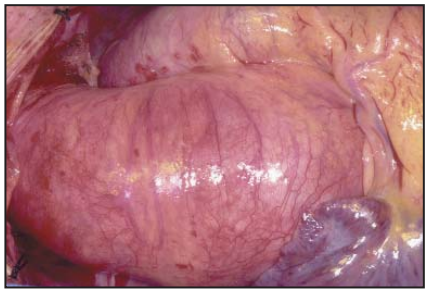


Figure 4. *Intraoperative photograph showing a markedly aneurysmal aortic root and arch.*

Figure 5. *A specimen of the resected ascending aorta notable for diffuse atherosclerosis.*

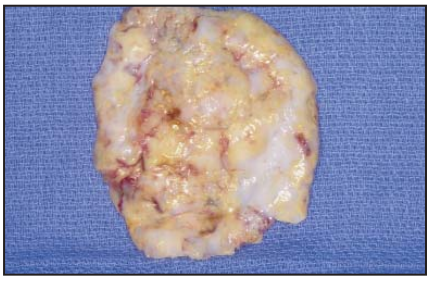
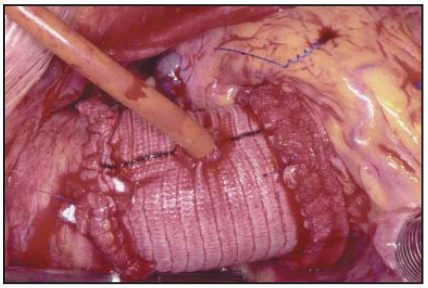


Figure 6. *Intraoperative photograph demonstrating successful ascending aortic aneurysm repair using a Hemashield graft.*



abnormal glucose metabolism and lipid disorders given their incidence, potential for morbidity, and long-term cardiovascular risk. The management of dyslipidemia in such a population should be based on guidelines of Adult Treatment Panel III of the National Cholesterol Education Program, which includes diet, exercise, and, if needed, use of statins and fibric acid derivatives to lower HIV-associated cholesterol and triglyceride levels.[19] Of note is that most statins are metabolized through the CYP3A4 pathway, which is inhibited by protease inhibitors, thus increasing the risk of skeletal muscle and hepatic toxicity.[20] Pravastatin appears to be the safest agent as it is least influenced by the CYP3A4 pathway.[19] An open question remains regarding when to start antiplatelet agents for primary prevention of cardiovascular disease in HIV-infected patients, given the baseline risk of vasculitis with HIV and secondary increased iatrogenic risk due to HAART. As HIV-infected patients live longer, traditional atherosclerotic disease will also become more prevalent and will necessitate aggressive risk factor modification and use of antiplatelet agents.

Evidence from the literature on antiretrovirals suggests that the complexity of the treatment regimen may have a negative impact on adherence.[21,22] It may be speculated that adding medications to an already extensive pill regimen in an attempt to prevent cardiovascular disease may reduce compliance with antiretrovirals. This can create a dire situation for patients on this treatment regimen. Many studies have shown that poor adherence to antiretroviral treatment regimens has serious consequences, including failure to prevent viral replication, an increased chance of developing viral resistance, the development of clinical complications, and shortened survival.[23-25] Future studies may help physicians better identify those patients who need to be treated to avoid opportunistic infections and those who will be harmed by cardiovascular complications due to therapy.

With the widespread use of protease inhibitors and prolonged survival of the AIDS population, we believe the observations made and the issues raised in this report will become increasingly important. Currently there are no guidelines that suggest screening for lipid disorders in younger HIV-infected patients on antiretroviral medications. However, given the propensity of such patients to develop accelerated lipodystrophy syndromes it may likely become a practice in the near future, with aggressive treatments of such disorders being carried out according to the NCEP recommendations. As there are no specific guidelines for HIV/AIDS, current National Cholesterol Education Program guidelines may in addition need to be amended to treat HIV/AIDS patients on HAART or with lipodystrophy syndrome as a high risk subset. Aggressive modification of other risk factors (notably smoking) is also probably indicated. ■

References

1. The Briefing Book on International Organizations in Geneva. Joint United Nations Program on HIV/AIDS. Available at : http://www.genevabriefingbook.com/chapters/unaids.html. Accessed August 27, 2003.
2. Barbaro G, Fisher SD, Lipshultz SE. Pathogenesis of HIV-associated cardiovascular complications. *Lancet Infec Dis*. 2001; 1:115–124.
3. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. Incidence of dilated cardiomyopathy and detection of HIV in myocardial cells of HIV-positive patients. *N Engl J Med*. 1998; 339:1093–1099.
4. Barbaro G, Di Lorenzo G, Grisorio B, Barbarini G. Cardiac involvement in the acquired immunodeficiency syndrome: a multicenter clinical-pathological study. *AIDS Res Hum Retroviruses*. 1998;14:1071–1077.
5. Heidenreich PA, Eisenberg MJ, Kee LL, et al. Pericardial effusion in AIDS: incidence and survival. *Circulation*. 1995;92:3229–3234.
6. Jenson HB, Pollock BH. Cardiac cancers in HIV-infected patients. In: Lipschultz SE, ed. *Cardiology in AIDS*. New York: Chapman and Hall; 1998:255–263.
7. Joshi VV, Pawel B, Conner E, et al. Arteriopathy in children with acquired immunodeficiency syndrome. *Pediatr Pathol*. 1987;7:261–275.
8. Chetty R, Batitang S, Nair R. Large artery vasculopathy in HIV-positive patients: another vasculitic enigma. *Hum Pathol*. 2000;31:374–379.
9. Sinzobahamvya N, Kalangu K, Hämel-Kalinowski W. Arterial aneurysms associated

Main Points

- The recent onset of the acquired immunodeficiency syndrome (AIDS) epidemic and its natural history of a short, virulent course leaves most clinicians unfamiliar with the cardiac manifestations of the disease.
- Vascular lesions have become more evident in human immunodeficiency virus (HIV)-infected patients and have extended the spectrum of indicator diseases in HIV infection well beyond the classic opportunistic infections and Kaposi's sarcoma.
- Patients with HIV infection on highly active antiretroviral therapy (HAART) should be screened for abnormal glucose metabolism and lipid disorders given their incidence, potential for morbidity, and long-term cardiovascular risk.
- Adding medications to an HIV patient's already extensive pill regimen in an attempt to prevent cardiovascular disease may reduce compliance with antiretrovirals.

with human immunodeficiency virus (HIV) infection. *Acta Chir Belg*. 1989;89:185–188.
10. Lai WW, Colan SD, Easley KA, et al. Dilation of the aortic root in children infected with human immunodeficiency virus type 1: the prospective P2C2 HIV multicenter study. *Am Heart J*. 2001;141:661–670.
11. Tabib A, Greenland T, Mercier I, et al. Coronary lesions in young HIV-positive subjects at necropsy. *Lancet*. 1992;340:730.
12. Capron L, Kim YU, Laurian C, et al. Atheroembolism in HIV-positive individuals. *Lancet*. 1992;340:1039–1040.
13. Constans J, Marchand JM, Conri C, et al. Asymptomatic atherosclerosis in HIV-positive patients: a case-control ultrasound study. *Ann Med*. 1995;27:683–685.
14. Henry K, Melroe H, Huebsch J, et al. Severe premature coronary disease with protease inhibitors. *Lancet*. 1998;351:1328.
15. Périard D, Telenti A, Sudre P, et al. Atherogenic dyslipidemia in HIV-infected individuals treated with protease inhibitors. *Circulation*. 1999; 100:700–705.
16. Carr A, Samaras K, Burton S, et al. A syndrome of peripheral lipodystrophy, hyperlipidaemia and insulin resistance in patients receiving HIV protease inhibitors. *AIDS*. 1998;12:F51–F58.
17. Hadigan C, Meigs JB, Wilson PWF, et al. Prediction of coronary heart disease risk in HIV-infected patients with fat redistribution. *Clin Infect Dis*. 2003;36:909–916.
18. Stein JH, Klein MA, Bellehumeur J, et al. Use of human immunodeficiency virus-1 protease inhibitors is associated with atherogenic lipoprotein changes and endothelial dysfunction. *Circulation*. 2001;104:257–262.
19. Dube MP, Sprecher D, Henry WK, et al. Preliminary guidelines for the evaluation and management of dyslipidemia in adults infected with human immunodeficiency virus and receiving antiretroviral therapy: recommendations of the Adult AIDS Clinical Trial Group Cardiovascular Disease Focus Group. *Clin Infect Dis*. 2000;31:1216–1224.
20. Piscitelli SC, Gallicano KD. Interactions among drugs for HIV and opportunistic infections. *N Engl J Med*. 2001;344:984–996.
21. Paterson DL, Swindells S, Mohr J, et al. Adherence to protease inhibitor therapy and outcomes in patients with HIV infection. *Ann Intern Med*. 2000;133:21–30.
22. Stone VE, Hogan JW, Schuman P, et al. Antiretroviral regimen complexity, self-reported adherence, and HIV patients' understanding of their regimens: survey of women in the HER study. *J Acquir Immune Defic Syndr*. 2001;28:124–131.
23. Miller LG, Hays RD. Adherence to combination antiretroviral therapy: synthesis of the literature and clinical implications. *AIDS Read*. 2000;10:177–185.
24. Gifford AL, Bormann JE, Shively MJ, et al. Predictors of self-reported adherence and plasma HIV concentrations in patients on multidrug antiretroviral regimens. *J Acquir Immune Defic Syndr*. 2000;23:386–395.
25. Arnsten JH, Demas PA, Farzadegan H, et al. Antiretroviral therapy adherence and viral suppression in HIV-infected drug users: comparison of self-report and electronic monitoring. *Clin Infect Dis*. 2001;33:1417–1423.