ST-elevation myocardial infarction due to a spontaneous thrombus in the left anterior descending artery in a young HIV-infected patient

HIV enfeksiyonlu genç bir hastada sol ön inen arterde spontan trombüs oluşumu sonucu gelişen ST yükselmeli kalp krizi

Mehmet Çilingiroğlu, M.D., Navneet Lather, M.D., Amir Youseff, M.D., Tarek Helmy, M.D.

University of Cincinnati Medical School, Section of Cardiology, Cincinnati, Ohio, USA

Summary – With increasing life expectancy due to highly active antiretroviral therapy (HAART), the spectrum of human immunodeficiency virus (HIV)-associated morbidity and mortality has shifted from opportunistic infections toward associated chronic medical conditions. We report on a 26-year-old female patient receiving HAART for HIV infection, who developed spontaneous thrombosis of the proximal left anterior descending (LAD) artery, resulting in acute ST-elevation myocardial infarction. She had none of the conventional risk factors for the development of coronary artery disease. Following diagnostic coronary angiography that showed a large (16x3.4 mm) spontaneous thrombus in the proximal LAD artery, percutaneous coronary intervention was performed with prior aspiration of the occluding thrombus and implantation of a bare-metal stent. The patient was discharged with instruction of appropriate medical therapy. This case highlights the association between immunosuppression with HAART, particularly protease inhibitors, and the development of accelerated atherosclerosis in patients with HIV infection.

Özet – Son zamanlarda gelişen yüksek etkinlikteki antiretroviral tedavi sayesinde artan yaşam süresine bağlı olarak, insan bağışıklık eksikliği virüsü (HIV) ile enfekte olmuş hastaların mortalite ve morbidite spektrumu fırsatçı enfeksiyonlardan daha çok kronik hastalıklara yönelme göstermiştir. Bu yazıda, HIV enfeksiyonuna yönelik yüksek etkinlikte antiretroviral tedavi görürken, sol ön inen arterin proksimalinde gelişen spontan koroner arter trombüsüne bağlı olarak ST yükselmeli kalp krizi geçiren 26 yaşında bir kadın hasta sunuldu. Hastada koroner arter hastalığı gelişimi ile ilgili olabilecek geleneksel risk faktörlerinin hiçbiri yoktu. Tanıya yönelik koroner anjiyografide, sol ön inen arter proksimalinde büyük bir spontan trombüs (16x3.4 mm) görülmesi üzerine, hastaya perkütan koroner girişim uygulandı ve tıkayıcı trombüs aspirasyonla çıkarıldıktan sonra hastaya çıplak metal stent yerleştirildi. Hasta, uygun ilaç tedavisi verilerek taburcu edildi. Sunulan olguda, HIV ile enfekte olan hastalarda yüksek etkinlikteki antiretroviral tedavinin, özellikle proteaz inhibitörlerinin immün sistemde yarattığı baskılama ile hızlanmış ateroskleroz gelişimi arasındaki ilişkiye dikkat çekildi.

Human immunodeficiency virus remains one of the leading causes of mortality between the ages of 25 to 44 years in the United States.[1] With the advent of highly active antiretroviral therapy, the average life expectancy of HIV patients has increased by several decades, making it a chronic disorder. Several epidemiological studies have shown that HIV infection is associated with the development of cardiovascular diseases such as dilated cardiomyopathy, pericarditis, pulmonary hypertension, and diastolic dysfunction.[2] Additionally, it has been suggested that premature atherosclerosis may occur in HIV-infected individuals independent of traditional coronary artery disease risk factors.[3] There are reports in the literature suggesting an increased risk for developing acute myocardial infarction among patients infected with HIV.[4,5]

Abbreviations:

AMI	*Acute myocardial infarction*
CAD	*Coronary artery disease*
CRP	*C-reactive protein*
HAART	*Highly active antiretroviral therapy*
HIV	*Human immunodeficiency virus*
LAD	*Left anterior descending*
PCI	*Percutaneous coronary intervention*
PI	*Protease inhibitors*

Received: February 17, 2010 *Accepted:* December 1, 2010

Correspondence: Mehmet Çilingiroğlu, M.D., 1630 Chicago Avenue Apt., 1313 Evanston, IL 60201 USA. . Tel: 0 01 513 417 38 89 e-mail: mcilingiroglu@yahoo.com

The pathophysiology of atherosclerosis in patients with HIV infection is very complex, including direct endothelial damage from viremia, a heightened overall state of inflammation from immune activation, higher prevalence and contribution from traditional atherosclerotic risk factors, and direct effects from HAART. The markers of inflammation such as C-reactive protein are elevated in some patients with HIV infection along with several other abnormalities, leading to increased risk for thrombosis in multiple organ systems including epicardial coronary arteries.[4,6-8]

We present a female patient receiving HAART for HIV infection, who developed spontaneous thrombosis of the proximal left anterior descending artery that presented as ST-elevation myocardial infarction. She was initially thought to have a respiratory pathology or an alternative diagnosis of acute myopericarditis.

CASE REPORT

A 26-year-old African-American female with a medical history of HIV infection and HAART for one year presented to our emergency room with recurrent atypical chest pain of two-day history. Her last CD4 count was 368 cells/mm^3. The constituents of HAART included atazanavir, ritonavir, and emtricitabine/tenofovir. She had none of the conventional risk factors for the development of CAD (No family history, LDL 86 mg/dl, HDL 71 mg/dl, BP 118/65 mmHg, no diabetes mellitus, and nonsmoker). She described the pain as a pressure-like sensation located in the middle of her chest, radiating to both shoulders. Cough and deep breathing further exacerbated the pain. The initial impression was acute bronchitis with a viral syndrome. Community-acquired pneumonia was ruled out with a chest x-ray. However, 12-lead electrocardiography obtained in the emergency room showed ST-segment elevations in the anterior and inferolateral leads. Cardiac markers were elevated (troponin I 1.48 ng/ml, normal range 0.00-0.04 ng/ml; CK-MB 44.5 ng/ml, normal range 0.0-2.4 ng/ml). Troponin I and CK-MB levels peaked to 31.98 ng/ml and 126.8 ng/ml, respectively, on day 1 before trending down subsequently. The patient was diagnosed to have ST-elevation myocardial infarction with a possible alternative diagnosis of acute myopericarditis. She was transferred to the catheterization laboratory to rule out any acute coronary obstruction.

Diagnostic coronary angiography was performed after giving the patient a loading dose of clopidogrel 600 mg and intravenous eptifibatide. Coronary angiography showed a large proximal LAD artery thrombus ~16 x 3.4 mm in size with evidence for embolization to the distal LAD (Fig. 1a-c). The left main, left circumflex, and right coronary arteries were an-

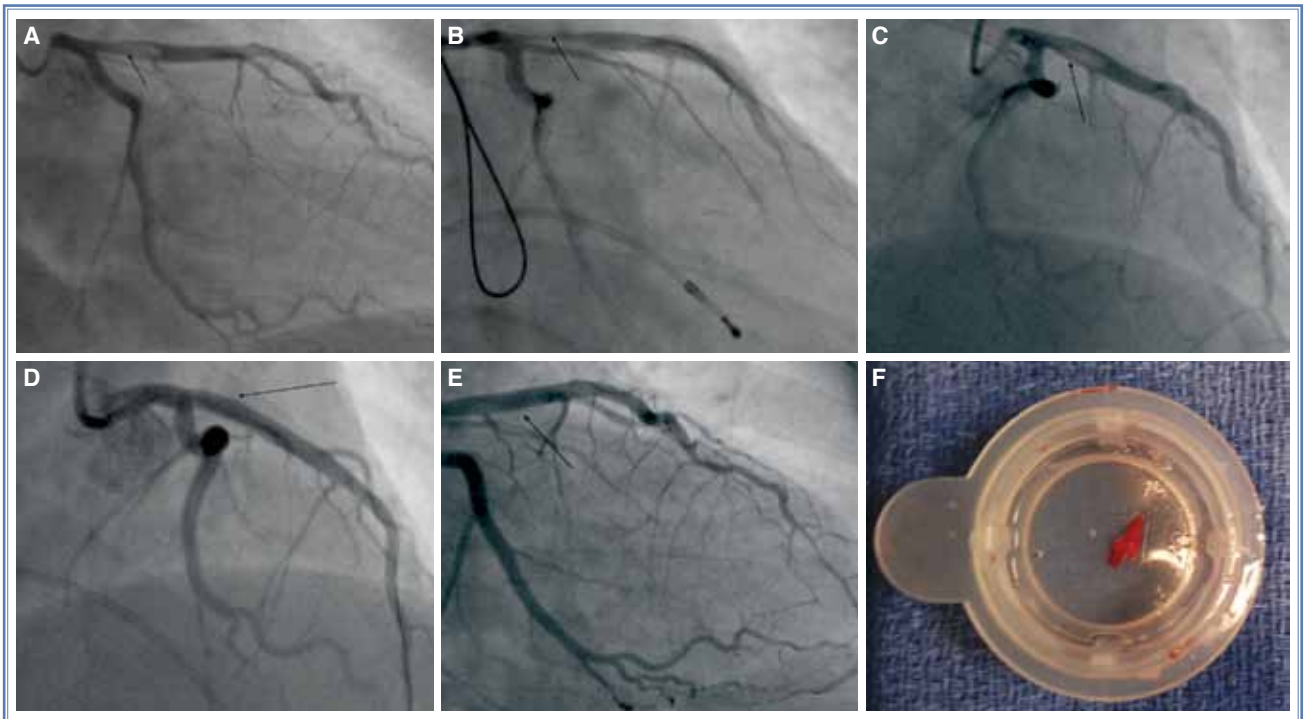

Figure 1. **(A, B)** Right anterior oblique caudal views and **(C)** cranial view of the LAD artery before PCI showing a large thrombus in the proximal segment with distal embolization (arrow). **(D)** Right anterior cranial and **(E)** right anterior caudal views showing TIMI 3 flow (arrow) following placement of a bare-metal stent in the LAD. **(F)** Thrombus aspirate from the proximal LAD.

giographically free of disease. Left ventriculography showed hypokinesis of the distal anterior apical wall with an estimated left ventricular ejection fraction of approximately 55%. Percutaneous coronary intervention was performed with the initial use of the Angio-Jet catheter to aspirate the occluding thrombus from the LAD. A temporary pacing wire was placed in the right ventricle before aspiration thrombectomy to prevent development of transient heart block secondary to release of adenosine from the clot and the vessel wall. Intracoronary glycoprotein IIb-IIIa with eptifibatide bolus (180 mcg/kg/min) was also given. Subsequently, a bare-metal stent, ~3.5 x 23 mm in size, was deployed with good angiographic results (Fig. 1d, e). Figure 1f shows a portion of the aspirated thrombus.

The patient was transferred to the coronary care unit for further care and monitoring. She was placed on antianginal medical therapy, which included metoprolol, enalapril, clopidogrel, eptifibatide (2 mcg/kg/min infusion), nitroglycerine, simvastatin, and aspirin. However, she continued to complain of recurrent chest pain with residual ST elevations on the electrocardiogram in the coronary care unit. Diagnostic coronary angiography performed the following day showed a small residual distal LAD artery thrombus. Vasospasm was also noted in the distal LAD artery, which was relieved by intracoronary nitroglycerine. No further coronary intervention was needed. Intravenous eptifibatide and heparin infusions were continued for 18 hours with subsequent resolution of her symptoms.

A retrospective inquiry showed no previous history of spontaneous thrombosis in the patient or her family members. As part of the diagnostic evaluation and to determine the etiology of acute coronary thrombosis, the hematology team was consulted. The recommended hypercoagulability workup showed no abnormal finding for antiphospholipid-anticardiolipin antibodies, homocysteine levels, factor V Leiden deficiency, prothrombin gene mutation, and antithrombin III levels. The patient was pain-free over the following two days. She was discharged home on the fifth hospital day and was instructed to continue clopidogrel for at least 12 months and aspirin indefinitely.

DISCUSSION

Atherosclerotic disease is a rising cause of major morbidity and mortality in HIV-infected patients. With increasing life expectancy due to HAART, the spectrum of HIV-associated morbidity and mortality has shifted from opportunistic infections toward associated chronic medical conditions such as CAD. Both HIV infection itself and various effects of HAART on the vasculature contribute to the pathogenesis of atherosclerosis.

Studies have suggested an approximate 1.5 to 2.0-fold increase in CAD in HIV-infected versus non-HIV-infected patients, with potentially larger differences for female HIV-infected patients in gender-stratified analyses.[4,6] A PubMed literature review with search terms 'HIV and thrombosis' yielded several reports of thrombotic events occurring in HIV-infected patients, including deep venous thrombosis, pulmonary embolism, portal and renal vein thrombosis, with the incidence of thromboembolic complications being in the range of 0.26% to 7.6%; a higher incidence was seen in patients with a low CD4 cell count, opportunistic infections, malignancy, or acquired immunodeficiency syndrome.[4] Various abnormalities account for the observed hypercoagulability in HIV-infected patients, including the presence of antiphospholipid antibodies/lupus anticoagulant, hyperhomocysteinemia, elevated factor VIII coagulant activity, decreased levels of natural anticoagulants/heparin cofactor II/antithrombin, increased levels of plasminogen activator inhibitor-1, von Willebrand factor and D-dimer, activated protein C resistance, and increased platelet activation.[4] These abnormalities correlated with the severity of HIV-related immunosuppression, as measured by CD4+ cell counts and the presence of concurrent infectious or neoplastic diseases.

Among HIV-infected patients, treatment with HAART containing protease inhibitors as in our patient has been particularly implicated in increased thromboembolic risk;[6,7] PI has been implicated in direct endothelial damage, which may be mediated by reduced nitric oxide production or release.[9] The development of CAD risk factors such as insulin resistance, hyperlipidemia, and fat redistribution syndrome may exacerbate already existing underlying atherosclerotic risk in patients using these medications. However, necropsy studies demonstrated premature CAD in HIV-infected patients even before the advent of PI, indicating that other mechanisms might be involved independent of these drugs.[10]

Primary HIV infection produces an underlying inflammatory state. Triant et al.[8] concluded that elevated CRP level and HIV infection were independently associated with increased AMI risk, in that HIV-infected patients with increased CRP levels had a 4-fold increased risk for AMI compared with noninfected patients. Although this study could not establish causality, it highlights the need for further in-depth evaluation of the prognostic value of CRP for CAD in HIV-

infected population. Therefore, measurement of CRP levels may be useful in the cardiovascular risk assessment of HIV-infected patients.[8]

Almost similar to our case, Saporito et al.[5] reported a case of AMI in an HIV-infected patient without significant CAD risk factors. The patient underwent rescue PCI, with a successful outcome. They also pointed out the possible role of HAART or direct viral effect on the development and progression of ischemic heart disease. They also proposed that the current approach to management of HIV-infected patients include close monitoring for CAD risk factors to improve prognosis and life expectancy in this patient population.[5] Another case study reported acute stent thrombosis that occurred within two days of PCI in an HIV-infected patient without a history of hypercoagulability.[4] The authors proposed that HIV-infected patients had predisposition to abnormal coronary artery pathology such as endothelial dysfunction, hypertriglyceridemia, and hypercoagulability.[4] Additionally, the introduction of PI as part of HAART further leads to the development of insulin resistance, fat redistribution syndrome, endothelial dysfunction, and hyperlipidemia. All these abnormalities contribute to accelerated atherosclerosis in this population already having an increased risk for atherosclerosis.

This presentation of a very young HIV-infected woman who developed ST-elevation myocardial infarction due to a large thrombus in the proximal LAD artery during treatment with PI primarily aims to highlight the increased risk for CAD in this young HIV-infected population. We emphasize the need for a very high degree of suspicion in these patients even when they present with atypical chest complaints, as there is a very high likelihood of overlooking a significant diagnosis such as AMI. Our case further confirms the available very limited number of case reports, which suggest the presence of accelerated atherosclerosis in young HIV-infected patients being treated with these life-prolonging medications. The development of CAD is most likely due to endothelial dysfunction, hyperlipidemia, insulin resistance, and hypercoagulability induced by these agents, in addition to the underlying increased risk associated with HIV infection itself. The inflammatory mediators such as CRP may have a potential to be used as markers of increased predisposition to thrombotic events in this population. Appropriate treatment of hyperlipidemia, cardiac risk factor modification, and perhaps careful drug selection for HAART will be helpful in better management of these patients. If possible, avoidance of PI and preferable use of nucleoside or non-nucleoside reverse transcriptase inhibitors would be a better option for these patients. At present, there appears to be no consensus on whether to include HIV as one of the conventional risk factors for CAD such as diabetes and hypertension. However, in the interim, we strongly suggest aggressive therapy for risk factor modification for prevention and control of CAD.

Conflict-of-interest issues regarding the authorship or article: None declared

REFERENCES

1. Centers for Disease Control and Prevention [Internet]. [cited 2010 May 12] HIV/AIDS Statistics and Surveillance. Available from: http://www.cdc.gov/hiv/topics/surveillance/index.htm.
2. Sudano I, Spieker LE, Noll G, Corti R, Weber R, Lüscher TF. Cardiovascular disease in HIV infection. Am Heart J 2006;151:1147-55.
3. Currier JS, Taylor A, Boyd F, Dezii CM, Kawabata H, Burtcel B, et al. Coronary heart disease in HIV-infected individuals. J Acquir Immune Defic Syndr 2003;33:506-12.
4. Ener RA, Palermo J, O'Murchu B, Burke JA, Wolf NM, Van Decker WA. HIV disease in thrombocardiology. J Invasive Cardiol 2007;19:235-9.
5. Saporito F, Micari A, Raffa S, Cerrito M, Micari G, Grassi R. Acute myocardial infarction and rescue percutaneous transluminal coronary angioplasty in a young HIV-infected patient. Int J Clin Pract 2005;59:376-8.
6. Currier JS, Lundgren JD, Carr A, Klein D, Sabin CA, Sax PE, et al. Epidemiological evidence for cardiovascular disease in HIV-infected patients and relationship to highly active antiretroviral therapy. Circulation 2008;118:e29-35.
7. Klein D, Hurley LB, Quesenberry CP Jr, Sidney S. Do protease inhibitors increase the risk for coronary heart disease in patients with HIV-1 infection? J Acquir Immune Defic Syndr 2002;30:471-7.
8. Triant VA, Meigs JB, Grinspoon SK. Association of C-reactive protein and HIV infection with acute myocardial infarction. J Acquir Immune Defic Syndr 2009;51:268-73.
9. Fu W, Chai H, Yao Q, Chen C. Effects of HIV protease inhibitor ritonavir on vasomotor function and endothelial nitric oxide synthase expression. J Acquir Immune Defic Syndr 2005;39:152-8.
10. Tabib A, Greenland T, Mercier I, Loire R, Mornex JF. Coronary lesions in young HIV-positive subjects at necropsy. Lancet 1992;340:730.

Key words: Angioplasty, balloon, coronary; antiretroviral therapy, highly active/adverse effects; coronary disease/etiology; HIV infections/complications; myocardial infarction.

Anahtar sözcükler: Anjiyoplasti, balon, koroner; antiretroviral tedavi, yüksek derecede aktif/yan etki; koroner hastalık/etyoloji; HIV enfeksiyonu/komplikasyon; miyokart enfarktüsü.