A Case Series of HIV-Seropositive Patients and Hypercoagulable State—Is It Difficult to Treat Even with Therapeutic Anticoagulation?

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Abstract

Patients with human immunodeficiency virus (HIV) are at risk of developing thrombosis and are 8 to 10 times more likely to develop thrombosis than the general population. Moreover, if they have hypercoagulable state they can have severe thrombosis and life-threatening thrombotic events. The purpose of this retrospective study is to analyze hypercoagulable state in HIV-seropositive patients who have been diagnosed with venous thromboembolism (VTE). This study is a subgroup study of a larger cohort group of HIV-seropositive patients with VTE followed up with our vascular medicine outpatient clinic. The patients included for this study were HIV-seropositive patients with hypercoagulable state, analyzed over the past 3 years, and followed prospectively. HIV-seropositive patients with arterial thrombosis were excluded. These patients had minimum, regular follow-up of 3 months, with a Doppler scan in the beginning and last follow-up. All the patients were analyzed for hypercoagulable state and the patients selected in this study were those who were tested positive for hypercoagulable state. All patients were analyzed for age, gender, race, site of thrombosis, coagulation factors, lipid panel, type of antiretroviral treatment, past or present history of infections or malignancy, CD4 absolute and helper cell counts at the beginning of thrombosis, and response to treatment and outcome. Patients with HIV with arterial thrombosis were excluded. The study was approved by the ethics committee. Five patients were included in this study. The mean age was 47.8 years (range 38 to 58 years). All were male patients with lower limb thrombosis. Most common venous thrombosis was popliteal vein thrombosis, followed by common femoral, superficial femoral, and external iliac thrombosis. Two patients had deficiency of protein S, two had high homocysteine levels, one had deficiency of antithrombin 3, and one had increase in anticardiolipin immunoglobulin G antibody. All the patients were taking nucleoside and nonnucleoside inhibitors but only one patient was taking protease inhibitors. There was no history of malignancy but two patients had past history of tuberculosis. The mean absolute CD4 counts were 244 cells/UL (range 103 to 392 cells/UL) and helper CD4 counts were 19.6 cells/UL (range 15 to 30 cells/UL). All were anticoagulated with warfarin or

Keywords

- ▶ deep vein thrombosis
- ▶ duplex
- ▶ DVT
- ▶ enoxaparin
- ▶ factor V Leiden
- ▶ low molecular weight heparin
- ▶ proximal

enoxaparin. There was complete resolution of deep vein thrombosis only in one patient on long-term anticoagulation but there was no resolution of thrombosis in the other four patients despite of therapeutic anticoagulation for more than 6 months. All the patients are alive and on regular follow-up. Thrombosis in HIV patients is seen more commonly in middle aged, community ambulant male patients. The most common hypercoagulable state was noted as deficiency of protein S and hyperhomocysteinemia. Eighty percent of the patients did not respond to therapeutic anticoagulation.

Human immunodeficiency virus (HIV) infection has twofold to 10-fold increased risk of venous thrombosis in comparison with a general population of the same age.¹⁻³ Venous thromboembolism (VTE) can develop in ambulatory patients with HIV infections or acquired immune deficiency syndrome (AIDS).⁴

The purpose of this study is to analyze the hypercoagulable state in HIV-seropositive patients having VTE and its respond to therapeutic anticoagulation.

Methods

This study is a subgroup study of a larger cohort group of HIV-seropositive patients with VTE followed up with our vascular medicine outpatient clinic.

The patients included for this study were HIV-seropositive patients with hypercoagulable state, analyzed over the past 3 years and followed prospectively. HIV-seropositive patients with arterial thrombosis were excluded.

These patients had minimum, regular follow-up of 3 months, with a Doppler scan in the beginning and last follow-up. All the patients were analyzed for hypercoagulable state and the patients selected in this study were those were tested positive for hypercoagulable state. All patients were analyzed for age, gender, race, site of thrombosis, coagulation factors, lipid panel, type of antiretroviral treatment, past or present history of infections or malignancy, CD4 absolute and helper cell counts at the beginning of thrombosis, and response to treatment and outcome. Patients with HIV with arterial thrombosis were excluded. The study was approved by the ethics committee.

Results

Five patients were included in this study. The mean age was 47.8 years (range 38 to 58 years). All were male patients with lower limb thrombosis. Most common venous thrombosis was popliteal vein thrombosis, followed by common femoral, superficial femoral, and external iliac thrombosis. Two patients had deficiency of protein S, two had high homocysteine levels, one had deficiency of antithrombin 3, and one had increase in anticardiolipin immunoglobulin G antibody. All the patients were taking nucleoside and nonnucleoside inhibitors but only one patient was taking protease inhibitors. There was no history malignancy but two patients had past

history of tuberculosis (TB). The mean absolute CD4 counts were 244 cells/UL (range 103 to 392 cells/UL) and helper CD4 counts were 19.6 cells/UL (range 15 to 30 cells/UL). All were anticoagulated with warfarin or enoxaparin. There was complete resolution of deep vein thrombosis only in one patient on long-term anticoagulation but there was no resolution of thrombosis in the other four patients despite of therapeutic anticoagulation for more than 6 months. All the patients are alive and on regular follow-up.

Discussion

Infection with HIV is an independent risk factor for developing venous thromboembolic events. The frequencies of these thrombophilic abnormalities increase with the progression to AIDS. Furthermore, autopsy studies reveal high rates of previously undiagnosed thromboembolism among patients with AIDS.⁵ All our patients were ambulant but had thrombosis possibly due to active prothrombotic state due to HIV.

There is increased incidence of thromboembolic events in the HIV-infected population after the introduction of highly active antiretroviral therapy (HAART), with the use of protease inhibitors in particular being implicated.⁶ In our study group, only one patient was on concomitant protease inhibitor therapy.

HIV is also associated with a variety of acquired coagulopathies that increase the incidence of venous and arterial thrombosis, including elevated antiphospholipid-anticardiolipin antibodies, elevated serum homocysteine levels, elevated lupus anticoagulant levels, elevated plasma factor VII activity, low levels of antithrombin III-activated protein C resistance, protein C deficiency, and protein S deficiency.^{7,8} There is a associated link between infection and thrombosis via endothelial activation has been suggested. Some small studies have shown decreased concentrations of both protein S and protein C in HIV-infected patients, whereas others have reported a prevalence of protein S deficiency among persons with HIV infection between 33 and 94%.⁸ A study of protein S deficiency among 25 randomly selected HIV-seropositive men followed up at the National Centre for Infectious Diseases, Atlanta, found 19 subjects (76%) with decreased plasma free protein S levels, and this was a statistically significant difference compared with healthy male controls.^{8,9} In our study, two patients out of five had deficiency of protein S.

Acquired protein S and protein C deficiency often develop in patients with HIV with acute opportunistic infections.

These deficiencies may be reversible after treatment of opportunistic infections. Forty-nine consecutive HIV patients with acute opportunistic infections for thrombophilic parameters followed them up after 8 weeks. In acutely ill patients, the incidence of protein S deficiency was 67% (33/49) and of protein C deficiency 25% (12/49). At the follow-up visit, the incidences were 54% (14/26) and 8% (2/26), respectively. Protein S and protein C levels increased significantly from initial to follow-up visit ($p < 0.05$). Three patients presented with deep venous thrombosis on admission, out of which two had protein S or protein C deficiency.⁹ In our study, out of the five patients with hypercoagulable state, only two had opportunistic infections, TB.

High levels of plasma homocysteine represent an independent risk factor for the development and progression of atherothrombotic vascular disease. Furthermore, evidence suggests that even moderately increased plasma homocysteine levels may trigger vascular disease. Between October 2004 and February 2005, 117 Italian HIV patients on HAART were assayed for plasma homocysteine levels and compared with 25 untreated HIV-infected patients and 60 age-matched local healthy blood donors. Mean plasma levels of homocysteine were 15.04 mmol/L in HIV patients on HAART, 13.08 mmol/L in HIV untreated patients, and 10.9 mmol/L in healthy controls ($p < 0.01$).¹⁰ In our study, out of five patients, two patients had high plasma homocysteine levels.

Limitations of Our Study

The sample size in our case series was small, but there were HIV patients with VTE with hypercoagulable state. Patients with arterial thrombosis were excluded in our study.

Conclusions

Venous thromboembolism in HIV-seropositive patients was seen more commonly in middle-aged, community ambulant

male patients. Lower limb thrombosis, with involvement of the popliteal vein, was the commonest. Protein S deficiency and hyperhomocysteinemia were the most common coagulation abnormalities in Asian population. Eighty percent of the patients did not respond to therapeutic anticoagulation, as evidenced by either no resolution or extension of the thrombus.

References

- 1 Bibas M, Biava G, Antinori A. HIV-associated venous thromboembolism. *Mediterr J Hematol Infect Dis* 2011;3(1):e2011030
- 2 Ahonkhai AA, Gebo KA, Streiff MB, Moore RD, Segal JB. Venous thromboembolism in patients with HIV/AIDS: a case-control study. *J Acquir Immune Defic Syndr* 2008;48(3):310–314
- 3 Klein SK, Slim EJ, de Kruif MD, et al. Is chronic HIV infection associated with venous thrombotic disease? A systematic review. *Neth J Med* 2005;63:129–136
- 4 Saif MW, Greenberg B. HIV and thrombosis: a review. *AIDS Patient Care STDS* 2001;15(1):15–24
- 5 Jacobson MC, Dezube BJ, Aboulafia DM. Thrombotic complications in patients infected with HIV in the era of highly active antiretroviral therapy: a case series. *Oxford Journals. Clin Infect Dis* 2004;39(8):1214–1222
- 6 Shen Y-M, Frenkel EP. Thrombosis and a hypercoagulable state in HIV-infected patients. *Clin Appl Thromb Hemost* 2004;10(3):277–280
- 7 Orlovic D, Smego A. Hypercoagulability due to protein S deficiency in HIV-seropositive patients. *RA Int J Collab Res Intern Med Public Health* 2009;1(6–7):187–193
- 8 Stahl CP, Wideman CS, Spira TJ, Haff EC, Hixon GJ, Evatt BL. Protein S deficiency in men with long-term human immunodeficiency virus infection. *Blood* 1993;81(7):1801–1807
- 9 Erbe M, Rickerts V, Bauersachs RM, Lindhoff-Last E. Acquired protein C and protein S deficiency in HIV-infected patients. *Clin Appl Thromb Hemost* 2003;9(4):325–331
- 10 Parruti G, Manzoli L, Di Iorio G, et al. Plasma homocysteine levels in an Italian cohort of HIV infected patients. *International AIDS society 2012; The 3rd IAS Conference on HIV Pathogenesis and Treatment. Abstract no. 2177530.*