

Risk of Venous Thromboembolism in Patients Infected with HIV: A Cohort Study

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Abstract

Introduction Human immunodeficiency virus (HIV) patients are at risk of developing thrombosis than general population. There are several intersecting mechanisms associated with HIV infection and antiviral therapy that are emerging, which may lead to vasculopathy and hypercoagulability in these patients.

Methods We analyzed the HIV patients who followed up with our Vascular Medicine outpatient clinic with venous thromboembolism (VTE) over the past 3 years and followed them prospectively. The patients included were those who had minimum, regular follow-up of 3 months, with a Doppler scan in the beginning and last follow-up. 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, response to treatment and outcome. Patients with HIV with arterial thrombosis were excluded.

Results A total of eight patients were analyzed. The mean age was 49.87 years (range, 38–58 years). All were male patients with six patients having lower limb thrombosis, one patient with upper limb thrombosis related to peripheral inserted central catheter (PICC), and one patient had pulmonary embolism with no deep vein 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 antibody. All patients were taking nucleoside and nonnucleoside inhibitors but only two patients were taking protease inhibitors. There was history of lymphoma in one and nonsmall cell lung carcinoma in one patient. Three patients had past history of tuberculosis and one of these patients also had pneumocystis carinii pneumonia. The mean absolute CD4 counts were 383.25 cells/UL (range, 103–908 cells/UL) and helper CD4 counts were 22.5 cells/UL (range, 12–45 cells/UL). All were anticoagulated with warfarin or enoxaparin. There was complete resolution of deep vein thrombosis in two patients

Keywords

- ▶ anticoagulation
- ▶ protein C
- ▶ protein S
- ▶ homocysteine
- ▶ antithrombin 3
- ▶ duplex
- ▶ enoxaparin
- ▶ risk factors

(one with PICC line thrombosis in 3 months and other with popliteal vein thrombosis in 1 year). There was extension of clot in one patient and no resolution in others. Seven patients are still alive and on regular follow-up.

Conclusion Thrombosis in HIV patients is seen more commonly in middle aged, community ambulant male patients. Left lower limb involvement with involvement of popliteal vein is most common. Deficiency of protein S and hyperhomocystenaemia were noted in these patients. Most of these patients did not respond to therapeutic anticoagulation, but the extension of the thrombosis was prevented in majority of cases.

Human immunodeficiency virus (HIV) infection has been recognized as a prothrombotic condition and is associated with a 2- to 10-fold increased risk of venous thrombosis in comparison with a general population of the same age.¹⁻³ There are several intersecting mechanisms associated with HIV infection and antiviral therapy that are emerging, which may lead to vasculopathy and hypercoagulability in HIV patients. Furthermore, these hypercoagulable states predispose them to severe thrombosis and potentially life threatening thromboembolic events.¹⁻³

VTE can develop in ambulatory patients with HIV infections or acquired immune deficiency syndrome (AIDS), who otherwise have no known risk factors for pathologic thrombus formation.⁴

The purpose of this study is to analyze the demographic data and risk factors predisposing to thrombosis and their relationship to the prognosis of venous thromboembolism (VTE) in HIV-seropositive patients.

Methods

Eight HIV-seropositive patients diagnosed with VTE were followed up in the Vascular Medicine outpatient clinic of Tan Tock Seng Hospital over a 3-year period, from March 1, 2008 to April 30, 2011. These patients were followed up at minimum 3 monthly intervals, with venous Doppler scans done at the beginning and on the last follow-up.

The medical records of these patients were obtained and data analyzed retrospectively for demographic features (age, gender, and race), site of thrombosis, lipid panel, CD4 absolute, and helper cell counts, coagulation factors (protein S, plasma homocysteine levels, anticardiolipin Immunoglobulin antibodies, and antithrombin 3 levels), type of antiviral treatment, presence of past or current history of infections or malignancies, and response and outcome to anticoagulant treatment. HIV-seropositive patients with arterial thrombosis were excluded.

The diagnosis of venous thrombosis was based on the findings of compressibility of the intraluminal thrombus by duplex ultrasonography performed at the vascular diagnostic laboratory of Tan Tock Seng Hospital. The thrombus was defined as completely resolved when the follow-up scan was normal and partially resolved if the thrombus became smaller but was still present. No resolution was defined as persistence of the thrombus while progression was defined as the thrombus showing an extension on the scan.

Results

All eight patients analyzed were community ambulant males, with the mean age being 49.87 years (range, 35–58 years). Seventy-five percent of patients were Chinese, 25% were Malays. Six of them were diagnosed with lower limb thrombosis, one with upper limb thrombosis related to a peripherally inserted central catheter (PICC) and one with pulmonary embolism in the absence of deep vein thrombosis. Amongst the venous thromboses, the most prevalent was popliteal vein thrombosis, followed by common femoral, superficial femoral, and external iliac thrombosis.

Two patients demonstrated deficiencies of protein S, two had elevated plasma homocysteine levels, one had increased levels of anticardiolipin IgG antibodies, and another had a deficiency of antithrombin 3 (►Table 1). Two had high triglyceride levels and another two had high low-density lipoprotein cholesterol levels.

All patients were on treatment with nucleoside reverse transcriptase inhibitors (NRTIs) and nonnucleoside reverse transcriptase inhibitors (NNRTIs), with two on concomitant protease inhibitor (PI) therapy.

One patient had a history of lymphoma while one had nonsmall cell carcinoma of the lung. Three patients reported a past history of tuberculosis (TB) and one of these patients also had pneumocystis carinii pneumonia. The mean absolute CD4 counts were 383.25 cells/UL (range, 103–908 cells/UL) and helper CD counts were 22.5 cells/UL (range, 12–45 cells/UL).

All patients were anticoagulated with warfarin or enoxaparin, with complete resolution of deep vein thrombosis documented in two. The one with peripherally inserted central catheter line thrombosis achieved complete resolution in 3 months whereas the other with popliteal vein thrombosis did so in 1 year. Clot extension was documented in one patient and there was no resolution in the rest. At the end of the study period, seven patients were still alive.

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.⁵ In patients with AIDS, as documented by CD4 cell counts $< 2 \times 10^8/L$, have a higher risk of thrombosis than

Table 1 Demographic and results data

Patient	1	2	3	4	5	6	7	8
Age in years	48	48	38	47	58	48	56	56
Gender	Male	Male	Male	Male	Male	Male	Male	Male
Race	Malay	Chinese	Malay	Chinese	Chinese	Chinese	Chinese	Chinese
Protein C (normal range, 70–150%)	N	N	N	N	N	N	N	N
Protein S (normal range, 65–130%)	N	N	N	21 ^a	N	41 ^a	N	N
Antithrombin 3 (normal range, 65–130%)	N	N	N	N	N	N	N	N
ACL-IgG (normal range, < 10 GPL U/mL)	N	N	N	27 ^b	N	N	N	N
ACL-IgM (normal range, < 10 MPL U/mL)	N	N	N	N	N	N	N	N
Lupus anticoagulant	Absent	Absent	Absent	Absent	Absent	Absent	Absent	Absent
Homocysteine (normal range, 5–15 µmol/L)	N	22 ^b	N	N	N	22 ^b	N	Not done
Factor V Leiden	N	Not done	N	N	N	Not done	Not done	N
CD-4 helper cells	12	20	18	30	15	15	45	25
CD-4 absolute count (cells/UL)	363	331	392	103	195	199	908	575
Malignancy	Lung Ca	Nil	Nil	Nil	Nil	Nil	Gastric lymphoma	Nil
Infections	TB, PCP	Nil	TB	Nil	Nil	TB	Nil	Nil

Abbreviations: N, normal; Ca, carcinoma; TB, tuberculosis; PCP, pneumocystis pneumonia.

^aLow.

^bHigh.

HIV-infected patients with a more robust immune system.⁵ In our patients, the mean absolute CD4 counts were 383.25 cells/UL (range, 103–908 cells/UL) and helper CD counts were 22.5 cells/UL (range, 12–45 cells/UL). Autopsy studies reveal high rates of previously undiagnosed thromboembolism among patients with AIDS.⁶

There is higher incidence of venous thrombosis in patients with active opportunistic infections or malignancy, and some epidemiological studies point to the increased incidence of thromboembolic events in the HIV-infected population after the introduction of highly active antiretroviral therapy (HAART), with the use of PI in particular being implicated.⁷ In our study group, all patients were on treatment with NRTIs and NNRTIs, with only two on concomitant PI therapy.

Thirty HIV patients followed up at Virginia Mason Haematology/Oncology clinic (Seattle) over a 6-year period, the median patient age at the time of thrombosis was 43 years.⁶ In another study, median age at thrombosis was 36 years.⁸ These evidence suggest that the age of onset of venous thrombosis in HIV patients tend to be younger than that of the general population, 62 years compared with the HIV cohort.^{6,8} In our study, the mean age being 49.87 years (range, 35–58 years).

HIV is also associated with a variety of acquired coagulopathies that increase the incidence of venous and arterial thrombosis, including elevated antiphospholipid-anticardio-

lipin 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.^{6,9} There is an 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, while others have reported a prevalence of protein S deficiency among persons with HIV infection between 33 and 94%.^{5,9} 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 patients (76%) with decreased plasma-free protein S levels, and this was a statistically significant difference compared with healthy male controls.¹⁰ The propensity for HIV patients to have decreased protein S levels is corroborated in our study, whereby 25% of the patients were documented to have decreased protein S levels in the presence of VTE.

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.¹¹ In our study, out of the four patients with opportunistic infections, three had TB and one of them had pneumocystis pneumonia and amongst these only one was protein S deficient.

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. 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 ($p < 0.01$).¹² In our study, where all the patients had VTE and were concomitantly on HAART, 25% had high plasma homocysteine levels.

HIV not only leads to depletion of CD4 cells during the course of disease, but induces polyclonal B-cell activation with marked hypergammaglobulinaemia, circulating immune complexes and anticardiolipin antibodies (ACA). ACA are antibodies belonging to a heterogeneous group of antibodies directed against negatively charged phospholipids and increased levels can be detected in both the sera^{13–15} and the cerebral spinal fluid¹³ in a significant proportion of HIV-infected patients. In patients with systemic lupus erythematosus, the presence of ACA is closely related to the occurrence of venous and arterial thromboses.¹⁶ However, evidence of an association to habitual abortion or thromboembolism as known in autoimmune conditions is lacking in HIV disease.^{14,17} In our study, one patient had increased levels of anticardiolipin IgG antibodies in the presence of VTE.

HAART regimens, especially those including PIs have shown to cause in a high proportion of HIV-infected patients metabolic (dyslipidaemia, insulin-resistance) and somatic (lipodystrophy/lipoatrophy) changes that in the general population are associated with an increased risk of cardiovascular disease (coronary artery disease and stroke).¹⁸ The effects of PI-containing HAART on metabolic and haemostatic parameters suggested that patients receiving PI-containing HAART had decreased fibrinolysis and increased coagulability, which may thus represent additional risk factors for cardiovascular disease in this patient group.¹⁹ PI could be a risk factor for venous thrombosis not due to thrombophilic abnormalities but likely related to abnormalities in platelets or endothelium.²⁰ In our study, two patients were on concomitant PI therapy.

Achieving optimal anticoagulation is challenging in patients with HIV. In a study, it was noted that the median percentage of international normalized ratio (INR) measurements of blood clotting time within the therapeutic range was 28.6%. Of those INRs outside the therapeutic range, 50.5% were subtherapeutic and 21.2% were supra-therapeutic, highlighting the potential difficulty in achieving adequate anticoagulation in patients on antiretroviral regimens, which may give rise to poor or nonresponse to anticoagulant therapy.²¹ In our study, as these patients were followed by specialized anticoagulation clinics, PTINR was therapeutic in 60 to 70% of HIV patients. However, only 25% of HIV patients responded well to anticoagulant therapy.

Limitations of Our Study

Despite an increased prevalence of HIV-seropositive patients with VTE, as compared with the general population, the case study population was small, with only eight patients. We

included and analyzed only VTE cases and those with concomitant arterial thrombosis were excluded, further reducing our sample size.

Strengths of Our Study

Data on HIV-seropositive patients with VTE are currently sparse especially in Asian setting. Ours is the *first* such study in Singapore analyzing demographic data and risk factors predisposing to venous thrombosis and their relationship to the prognosis of VTE in HIV-seropositive patients. The information gathered may be useful to local clinicians in the management of HIV patients with VTE. By excluding HIV-seropositive patients with arterial thrombosis, our analysis was more focused with pure VTE.

Conclusions

VTE in HIV-seropositive patients was seen more commonly in middle-aged male patients. Surprisingly, all patients were community ambulant. This is compared with VTE in general population, majority of whom have immobilization as a predisposing factor for VTE.

Lower limb thrombosis, with involvement of the popliteal vein was the commonest. Predisposing factors in our Asian population were protein S deficiency and hyperhomocysteinemia, which are well documented in Western population with HIV and thrombosis. It is difficult to treat these patients with therapeutic anticoagulation and the ongoing thrombotic state does not easily help in the resolution of thrombus in majority of patients but limits the progression of the thrombus.

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