Case Report

Human Immune-deficiency virus associated deep vein thrombosis coexisting with venous ulcer

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Abstract

Human immune-deficiency virus (HIV) infection is known to be a prothrombotic condition especially when advanced and characterized by low CD4+ count and high viral load, and treated with protease inhibitor(s). In such cohort of HIV infected patients the prevalence of deep vein thrombosis is up to 10-fold of that found in the general population.This is the case report of a 48-year old man with advance HIV infection with associated left leg venous ulcer who was receiving a protease inhibitor presenting with left lower extremity deep vein thrombosis. He was admitted, evaluated, investigated and treated with low molecular weight heparin (Enoxaparin) and warfarin, and non-pharmacologic supportive therapy while on his highly active anti-retroviral therapy (HAART). After three weeks on inpatient treatment, the venous ulcer healed and the deep vein thrombosis resolved. The patient was discharged to continue warfarin for six months and has remained well 30 months since discharge. The prevalence of deep vein thrombosis is about 10-fold greater in HIV infection but the treatment remains same as in non-HIV infected patients.

Keywords: *Deep vein thrombosis, HIV infection*

Introduction

Human immune-deficiency virus (HIV) infection is one of the known independent risk factors for deep vein thrombosis (DVT) and this has made DVT to occur 2 – 10 times more common in HIV infected patients than in non HIV infected cohort. [1] Many factors have been identified to be responsible for this. These include influence of HIV infection on clotting factors, adhesiveness of endothelium, platelet hyper-activation and induction of other pro-inflammatory factors. [2] Globally HIV associated DVT cases are estimated at 2.6 / 1000 person years. [1] HIV associated DVT usually occurs in HIV infected patients older than 45years with AIDS who are on protease inhibitor like indinavir, and are being hospitalized. [1] Most of these patients do not necessarily have risk factors of DVT and the risk of venous thrombo-embolism (VTE) is irrespective of absence of other risk factors such as immobility, advanced age, cigarette smoking, pelvic trauma or surgery, pregnancy, oestrogen therapy and personal or family history of DVT. [1-3]

The pathogenetic mechanisms of HIV associated DVT involve protein C and protein S deficiency, low anti-thrombin levels, elevated factor VIII levels, elevated homocysteine levels and presence of anti-phospholipid antibodies all induced by the viral antigens. [3] All reported series have documented satisfactory outcome with anticoagulant therapy. [1] This case report being the first from our centre is to increase awareness on the existence of this condition in this state with a relatively high prevalence of HIV infection in the country.

Case report

This is a case report of a 48 year old banker diagnosed as having HIV infection in 2005. He presented in November 2010

with one week history of progressive painful left lower limb swelling and three weeks of left leg ulcer. The swelling started from the leg and progressed to involve the thigh. There was associated moderately severe non-radiating dull pain in the calf that was aggravated by walking and relieved by resting of the leg. There was no antecedent history of trauma to the limb, prolonged immobilisation, surgical operation or a recent long distance travel. The patient was diagnosed as having HIV infection from heterosexual route five years prior to this incident and has since then been on HAART, the current regimen being Tenofovir (245mg once daily), Emtricitabine (200mg once daily) and Efavirenz (600mg once daily) to be taken for life, although with poor adherence and compliance. He is not taking intravenous drugs of addiction. He developed a recurrence of left leg ulcer two weeks prior to the onset of the progressive left leg swelling. The first episode of leg ulcer was three years after his diagnosis of HIV infection, and has been occurring and healing on both legs alternately. He is not a known hypertensive, diabetic or sickle cell disease patient. There were no symptoms of AIDS defining infections or cancers in the patient.

Examination showed a middle aged man, who was not obese, not pale, not jaundiced, and not febrile. There were mildly enlarged discrete lymph nodes in both axillae and inguinal regions. The right lower limb showed scars of healed leg ulcers, while the left lower limb showed a granulating sloping edged superficial ulcer proximal to the medial malleolus measuring 8cmX6cm in diameter. The left lower limb was also swollen from foot to thigh and measurement showed increment in left lower limb diameter taken at equivalent points on both sides to be 7cm on the leg and 10cm on the thigh. There was no left calf tenderness, positive Homan's sign or differential warmth. The femoral, popliteal and dorsalis arterial pulses were palpable but weaker than the contralateral pulses. There were no varicosities of lower limbs' veins. Systemic examination was normal.

A doppler ultrasound of the left lower limb showed hyper-echoic filling defects and non compression of the common femoral, superficial femoral and popliteal veins. Doppler interrogation of the left lower extremity common femoral vein, superficial femoral vein and popliteal vein showed no spectral signal. There was low velocity signal and augmentation in the posterior and anterior tibial veins. (Fig 1)

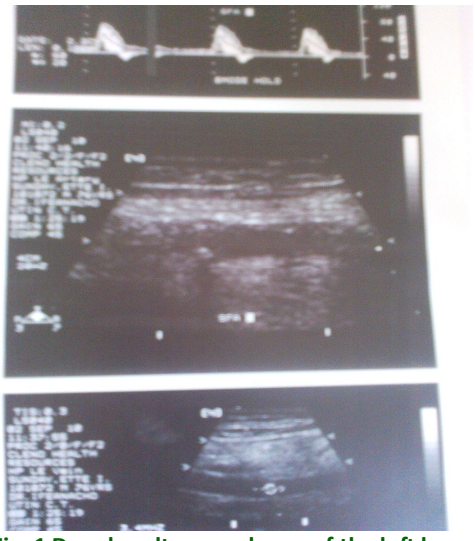

Fig. 1 Doppler ultrasound scan of the left lower limb veins of the patient showing thrombosis

Arterial doppler of the lower limbs showed normal colour flow mapping and spectral signal. The CD4 count was <200/µL while the viral load was 120,000 copies/cmm. His full blood count, lipid profile, fasting blood sugar, liver function test and renal function test were all normal. His clotting profile was also normal with prothrombin time ratio (international normalised ratio INR) of 1.2. A diagnosis of HIV associated left lower limb deep vein thrombosis co-existing with left leg venous ulcer was made. He

was admitted for treatment. The left lower limb was elevated on one pillow, subcutaneous injection of enoxaparin 40mg twice daily, warfarin tablet 5mg daily and cellulose dressing of the ulcer was started. The Enoxaparin injection was discontinued after 5 days when the target I.N.R. of 2.5 was achieved and anticoagulation was continued with warfarin tablet 5mg daily and aspirin tablet 75mg daily. After 21 days of inpatient treatment the left lower limb swelling resolved and the ulcer healed, and he was discharged home to continue treatment and follow up in our outpatient clinic. The anticoagulation was maintained with daily 5mg of warfarin tablet and 75mg of aspirin for six months and has since remained free of symptoms 30months after. During the six months of anticoagulation he underwent weekly clotting profile testing. He also underwent a repeat Doppler ultrasound scan of the lower limbs veins which showed normal appearance.

Discussion

Statistically DVT in HIV/AIDS is approximately 10 times greater than in the general population. [4] Treatment with highly active antiretroviral therapy (HAART) has successfully prolonged the life expectancy of HIV-infected patients and infection with the human immunodeficiency virus is increasingly becoming a chronic disease in the developed world. [4] Improved survival has been followed by an increased and anticipated prevalence of non-AIDS related conditions, including cardiovascular disease which is now a leading cause of morbidity and mortality among HIV-infected people. [4] This reported patient had been having recurrences of venous ulcers for two years and later DVT necessitating his presentation to hospital.

HIV infection has been recognized as a prothrombotic condition and this association has now been proven by a large number of studies. [1-4] The DVT in this patient was attributed solely to HIV infection and its treatment since there were no other risk factors of DVT found in the patient. Several specific factors are thought to be associated with DVT in patients with HIV. These can be grouped in three categories: those regarding the host, mainly defining a hypercoaglulable state and endothelial dysfunctions, those regarding the HIV diseases state, and those regarding the therapy. [4] In this patient the last two groups apply.

The frequency of VTE is higher in the presence of lower CD4+ cell counts, [5] and this could have been the cause of DVT in this reported patient who had a low CD4+ count of <200/µL. One group of authors concluded that a higher viral load, and lower CD4+ cell count, was associated with a higher risk of thrombosis. [6] This patient was also noted to have a high viral load which is also thought to be responsible for the DVT. Therefore by the definition of high viral load and low CD+ count this patient had advanced HIV infection. [5] The concomitant presence of advanced HIV disease and opportunistic infections like Cytomegalovirus and Pneumocystis jiroveci pneumonia (PCP) and Mycobacteriumavium-intracellulare appears to be an additional risk factor for thrombosis, [6] although our patient did not seem to have any opportunistic infection at the time of presentation. Mycobacterium is known to be able to activate macrophages directly and induces them to produce cytokines, especially TNF-α, IL-1 and IL-6. TNF-α and IL-1 blocks the protein C anticoagulant pathway and can elicit tissue factor production on endothelium and monocytes. IL-6 can also stimulate new platelets formation which have increased sensitivity to thrombin

activation and increased pro-coagulant activity. [6]

HAART and in particular the use of protease inhibitors (PI) have been associated with thrombotic events. [7] PI are thought to interfere with hepatic metabolism, specifically cytochrome P450 metabolism, and regulation of thrombotic proteins downregulate the anticoagulant effect within the body or generate endothelial or platelet dysfunction. [7-10] This reported patient's HAART included a protease inhibitor (tenofovir) and is believed to have played some synergistic role in the pathogenesis of DVT in this case. Consistent data exist connecting protease inhibitors with lipodystrophy, and HIV-positive individuals with fat redistribution may be at increased risk for developing an abnormal coagulation profile, such as increased fibrinogen, D-dimer, plasminogen activator inhibitor-1, or protein S deficiency. [7-10] However none of these could be assayed in this case. There were no clinical features suggestive of malignancy in the patient which has also been discovered to be responsible for VTE in HIV infected patients. [11]

This reported patient had thrombosis in the popliteal and femoral veins (Fig. 1) which conformed to the reports from other series. [1-4] Just as it was in this case, the management of proven VTE in HIV-infected patients should be the same as for the non HIV-patients, including long-term prophylaxis with low molecular weight heparin and warfarin for patients with recurrent thrombosis. [1, 4] In this case the patient was on anticoagulant therapy for six months and has not had recurrence. Interactions between warfarin and antiretrovirals is possible, given the influence of many antiretrovirals on CYP2C9 the enzyme responsible for the metabolism of the more active S-enantiomer of warfarin therefore the need for meticulous monitoring of therapy using the international normalised ratio (INR). [12, 13] It therefore behove the physician to be more meticulous with the monitoring of such patients while on anticoagulant therapy. Because of this weekly INR was used to monitor anticoagulation in this reported patient where equivalent dose of warfarin was appropriate for maintenance of optimal anticoagulation of INR of 2-3 times normal.

References

1. Damiyam CA, Iroezindu MO, Agaba EI, Awang SK, Ugoya SO, Shehu N. HIV associated deep vein thrombosis: case report from Jos, Nigeria. Niger Med J 2011;52:141-143.
2. Saber AA, Aboolian A, laRaja RD, Baron H, Hanna K. HIV/AIDS and the risk of deep vein thrombosis: a study of 45 patients with lower extremity involvement. Am Surg 2001;67:645-647.
3. Bissuel F, Berruyer M, Causse X, Dechavanne M, Trepo C. Acquired protein S deficiency: correlation with advanced disease in HIV-1 infected patients. J Acquired Immune Defic Syndr 1992;5:484-489.
4. Bibas M, Biava G, Antinori A. HIV-Associated Venous Thrombo embolism. Mediterr J Hematol Infect Dis 2011;3:(1):e2011030.doi: 10.4084/ MJHID.2011.030. Epub 2011 Jul 8.
5. Shen YM, Frenkel EP. Thrombosis and a hypercoagulable state in HIV-infected patients. Clin Appl Thromb Hemost 2004 Jul;10(3):277-80.
6. Ambrosetti M, Ferrarese M, Codecasa LR, Besozzi G, Sarassi A, Viggiani P, Migliori GB. Incidence of Venous Thromboembolism in Tuberculosis Patients. Respiration 2006;73:396.

7. George SL, Swindells S, Knudson R, Stapleton JT. Unexplained Thrombosis in HIV-infected Patients Receiving Protease Inhibitors: Report of Seven Cases. Am J Med 1999;107:624-6.
8. Crum-Cianflone NF, Weekes J, Bavaro M. Thromboses among HIV-infected patients during the highly active antiretroviral therapy era. AIDS Patient Care STDS 2008 Oct;22:771-8.
9. Deeks SG, Phillips AN, HIV infection, antiretroviral treatment, ageing, and non-AIDS related morbidity. BMJ 2009;338:288-292.
10. Lijfering WM, Ten Kate MK, Sprenger HG, Van der Meer J. Absolute risk of venous and arterial thrombosis in HIV-infected patients and effects of combination antiretroviral therapy. J Thromb Haemost 2006;4:1928-30.
11. Kaufmann T, Nisce LZ, Metroka C. Thromboembolism in AIDS-related Kaposi's sarcoma. JAMA 1991;266:2834.
12. Bonora S, Lanzafame M, D Avolio A, Trentini L, Lattuada E, Concia E, Di Perri G. Drug interactions between warfarin and efavirenz or lopinavir-ritonavir in clinical treatment. Clin Infect Dis 2008;46:146-7.
13. Fulco PP, Zingone MM, Higginson RT. Possible antiretroviral therapy–warfarin drug interaction. Pharmacotherapy 2008;28:945-9.

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