Case Report

# Deep Vein Thrombosis Following Enteric Fever & Immunological Failure in HIV Positive Soldier: Case Report

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## ABSTRACT

Incidence of deep vein thrombosis (DVT) is 2-10 times more in human immunodeficiency virus (HIV)-infected persons than non-HIV cohort. Risk factors involved with DVT in HIV-infected patients are age older than 45 years, use of protease inhibitor in highly active antiretroviral therapy (ART), most common indinavir, hospitalization and presence of AIDS-defining opportunistic infections such as cytomegalovirus, *Pneumocystis jiroveci* (is a yeast like fungus particularly in immune-compromised host), and *Mycobacterium*-intracellular. Others well known thrombogenic risk factors include are such as immobility, cigarette smoking, advanced age, pregnancy, pelvic surgery, and personal or family history of DVT may be absent in HIV-infected patients presenting with DVT. Inflammation and venous thrombosis are related to each other, and the associations between them are strong when the inflammation or the infection has occurred recently, or the inflammation is active. A 29-year-old HIV-positive soldier on first line ART with poor adherence presented with fever pain abdomen and diarrhea and was diagnosed to have an enteric fever with immunological and clinical failure. He was treated for enteric fever but during treatment of enteric fever he complains of painful left lower limb swelling after 4 weeks and was suspect to have DVT of left lower limb based on Doppler studies. After confirmation of DVT by Doppler images, thrombolytic therapy was started, and gradually improvement was seen in the condition. Recent Infection or inflammation has a strong association with the development of thrombosis in HIV-positive patients, absent with classical predisposing factors of DVT. Physicians involved in the care of HIV-positive patients should be aware of this condition and the associated aggravating risk factors in them so as to provide timely management.

**Key words:** Deep vein thrombosis, enteric fever, immunological failure, highly active antiretroviral therapy, human immunodeficiency virus

## INTRODUCTION

Thrombosis is another word for blood clot is a process of obstructive clot formation due to end product of imbalance of procoagulant, anticoagulant, and fibrinolytic factors. Venous thrombosis commonly known as deep vein thrombosis (DVT) refers to formation of a blood clot in one of the deep veins of the body (calf, thigh, Iliofemoral venous system, or in combination of any of these), usually a vein in the muscle of one of the legs.

Two types of thrombosis are distinguished:

- Non-occlusive thrombosis: Which does not completely block a vein
- Occlusive thrombosis: Which does completely block a vein.

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A blood clot or thrombosis may not be noticed or produce symptoms until it completely occludes with a vein. In human immunodeficiency virus (HIV)-infected persons, DVT occurs 2-10 times more common than in non-HIV infected cohort and globally HIV-associated DVT cases are estimated to be 2.6/1000 person.[1] Some studies of average quality have documented the absolute risk of venous thrombosis to be 5.7-11.3/1000 person which is much higher than incidence of 1/1000 person in the general population.[2] HIV infection is an independent risk factor for DVT, and it affects the process of thrombogenesis by few influencing factors and factors involved in the thrombus formation such as adhesiveness of endothelium, platelet hyperactivation, clotting factors, and induction of pro-inflammatory factors.[3]

Age is most important risk factor involved with DVT in HIV-infected patients of older than 45 years. Few other factors involved are use of protease inhibitor in highly active antiretroviral therapy (HAART), most common indinavir, hospitalization and presence of AIDS-defining opportunistic infections such as cytomegalovirus, *Pneumocystis jirovecii*, and *Mycobacterium*-intracellularly.[1] Other recognized thrombogenic risk factors such as immobility, cigarette smoking, advanced age, pregnancy, pelvic surgery and personal or family history of DVT may be absent in HIV-infected patients presenting with DVT.[1,3,4]

Risk factor for DVT:
- Inheritance of blood clotting
- Prolonged bed rest
- Damaged vein e.g., vasculitis
- History of episode of previous DVT
- Lack of movement
- Cancer
- Hormone replacement therapy
- Cardiovascular problems
- Obese and pregnant women
- Age more than 40 years

Principal three factors for DVT are:
1. Venostasis- stagnant or reduced flow of blood
2. Injury to blood vessels wall
3. Hyper-coagulability.

Characteristic symptoms include:
- Chronic leg pain
- Swelling, superficial phlebitis
- Venous stasis
- Leg ulcer
- Difficulty in walking perhaps impossible
- Post-thrombotic syndrome
- Chronic venous insufficiency and venous obstruction
- Cellulitis, Baker's cyst
- Hematoma or fracture
- Acute arterial hematoma.

DVT can be classified as:
- Primary or idiopathic: No cause is found
- Secondary: Recognized risk factor is found
- Hereditary/inherited
  - Antithrombin deficiency
  - Protein C deficiency
  - Protein S deficiency
  - Factor-V Leiden
  - Prothrombin
  - Factor XIII
  - Fibrinogen.
- Acquired
  - Immobilization
  - Plaster cast
  - Trauma
  - Major surgery
  - Orthopaedic surgery
  - Malignancy
  - Antiphospholipid syndrome
  - Myeloproliferative disorder
  - Polycythemia vera
  - Central venous catheter
  - Age and obesity
  - Hormonal replacement therapy.
- Mixed
  - High level of factor VIII
  - High level of factor IX
  - High level of factor XI
  - High level of fibrinogen
  - High level of thrombin activatable fibrinolysis inhibitor
  - Low level of tissue factor inhibitor pathway
  - Hyperhomocysteinaemia
  - High level of protein C inhibitor.

HIV is a public health concern in typhoid (enteric fever) endemic area.[5,6] A study in Peru has found typhoid fever to be 60 times more common in HIV-infected patients than in the general population probably due to lack of antibacterial activity in hosts and increased feco-oral route of transmission in homosexuals.[7] Due to lack of studies in typhoid endemic areas, the effect of incidence of HIV with incidence of enteric fever is poorly determined.[8,9]

At the site of localization of *Salmonella typhi* endotoxins are produced which releases array of cytokines including tumor necrosis factors, Interferon and arachidonic acid metabolites[9] that handle various clinical manifestations including thrombosis.[10]

Inflammation and venous thrombosis are related to each other, and the association between them are strong when the inflammation or the infection have occurred recently or the inflammation is active (flare-up).[11] In HIV infection, the pathogenesis in DVT involves protein C and S deficiency, low antithrombin levels, elevated homocysteine levels, and the presence of antiphospholipid antibodies that are induced by viral antigens.[4]

## CASE REPORT

A 29-year-old soldier was detected to have HIV-positive status in 2010 with an initial CD4 count of 565 cells/cumm with no history of any oportunistic infection at time he visit in outpatient department (OPD). He was asymptomatic and in WHO clinical Stage 1. Thereafter he was in regular follow-up with ART center. In October 2012, he was started on HAART (zidovudine AZT + 3TC lamivudine + nevirapine [NVP]) when his CD4 count dropped to 354 cells/cumm. In 2013, he developed pulmonary tuberculosis when he presented with fever and constitutional symptoms with resolving nonhomogenous opacity in right lower lung zone on chest X-ray (CXR). His sputum for acid-fast bacilli was negative but had an immunological failure due to poor adherence to HAART with CD4 count of 188 cells/cumm. He was started on ATT for 6 months with modified ART (EFV replaced NVP) and cotrimoxazole prophylaxis. Thereafter on follow-up he had an immune recovery with 6 monthly CD4 count of 304 cells/cumm in Jan 2015, 334 cells/cumm in July 2014 and 333 cells/cumm in Feb 2015. He was continued AZT+3TC+NVP regimen of HAART.

In May 2015, he presented to us with complaints of diarrhea due to small bowel disease and moderated to a high-grade continuous fever of 2 weeks duration. During clinical Investigation associated pain epigastrium with nausea and dysuria was found.

On physical examination, he was hemodynamically stable with signs of mild dehydration. He was febrile with the body temperature of 103°F. Oral cavity showed thrush with coated tongue and faint maculopapular erythematous blanch able rash over the body. Systemic examination was unremarkable.

On investigation his hemoglobin was 13.6 g/dl, total leukocyte count-3,600/cumm, P82L13, platelet count-66,000/cumm. He had prerenal azotemia with blood urea 48 mg/dl, creatine-2.1 mg/dl and hematocrit of 49%. CXR posterioranterior view showed bronchiectasis and pleural thickening right lower lung zone (old Koch infection sequelae), rapid test for malaria and peripheral blood smear for malarial parasites was negative. Dengue card test was negative. Ultrasonography (USG) abdomen was normal, serum electrolytes were normal, WIDAL was positive with >1:320 titer for O antigen and 1:160 titer for H antigen. Typhidot immunoglobulin M (IgM) was positive also. Urine routine examination (RE) showed 2-3 pus cells and liver function test was normal. Stool RE/Ova/cyst-NAD. His CD4 count was 172 cells/cumm.

His clinical diagnosis supported by lab investigations made us start ceftriaxone with Azithromycin being immunocompromised for enteric fever along with fluid rehydration to see the response in azotemia. His first line ART was continued along with cotrimoxazole prophylaxis and oral candidiasis treatment as his adherence to HAART was <95% for last 2 months.

He responded symptomatically after 5 days of therapy by becoming afebrile and clinically better. His azotemia resolved to standard values, and his platelet count reached 1,28,000/cumm when discharged on 9/6/15.

He reported to us again on 16/6/15 with complaints of a 1 week history of progressive painful left lower limb swelling. The swelling started from the leg and progressed to involve the thigh. There was associated dull pain in left calf which was aggravated by walking and relieved by leg rest or limb elevation.

On examination of the limbs left lower limb was swollen from foot to thigh and measurement showed increment in girth on equivalent points on both sides. There was calf tenderness, and Homan sign was positive. Local temperature of the limb was not raised. The femoral, popliteal and dorsal arterial pulses were palpable but weaker than the contralateral pulses. There were no varicosities on the limbs, and systemic examination was normal.

His routine hematological and biochemical parameters were normal. Bilateral venous Doppler of left lower limb was carried out which showed hypoechoic thrombus in left common femoral, superficial femoral and left popliteal vein up to trifurcation. Superficial thrombus extended up to common iliac vein till bifurcation at inferior vena cava. Also, thrombus extension was seen in great saphenous vein up to mid 1/3 thigh and short saphenous vein in upper 1/3 [Figures 1 and 2].

D-dimer was strongly positive with the value of 10176 ngFEU/ml (<855 is normal). His prothrombotic work up was done which showed average values of antiphospholipid (IgG/IgM), antithrombin-III (Ag), factor VIII, lupus anticoagulant screen, protein C, protein S, factor V, homocysteine levels.

He was diagnosed as proximal DVT left lower limb and was started on Injection enoxaparin with an overlap of warfarin (5 mg) for five days and thereafter continued warfarin titrating the dosage with target INR of 2.5. Due to a probable interaction of warfarin with nonnucleoside reverse transcriptase inhibitor (NVP) in HAART and cotrimoxazole, meticulous titration of a dose of warfarin was required to achieve target INR in this case. Limb stocking was applied to prevent post-thrombotic phlebitis and watch for signs of pulmonary thromboembolism was carried out.

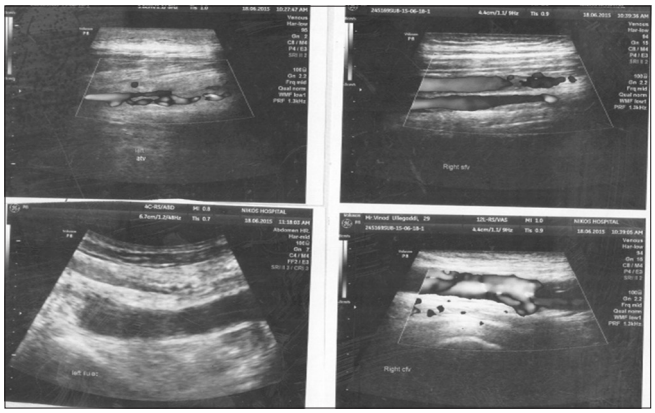

**Figure 1:** Thrombus in left iliac vein

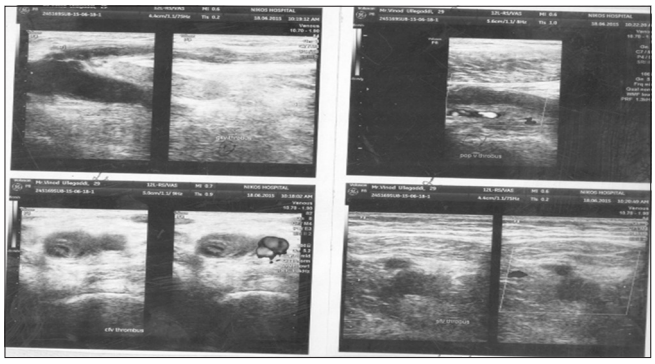

**Figure 2:** Thrombus in left superficial femoral vein, common femoral vein and left popliteal vein

His lower limb swelling and pain responded gradually to the treatment, and symptomatic improvement was evident. Repeat Left lower limb venous Doppler on 22/7/15 showed partial canalization in deep veins left leg (left iliac, external iliac, common femoral vein) with usual great saphenous vein but total occlusion in superficial femoral vein is still present. His serum, D-dimer was 897 ngFEU/ml (<855) on 17/7/15.

## DISCUSSION

HIV infection is a prothrombotic condition and is independently a risk factor for DVT.[1,3,4,12] Associated risk factors of thrombogenesis in HIV-infected patient can coexist and increases the incidence of DVT as age older than 45 years, use of protease inhibitor in HAART (most commonly indinavir), hospitalization and presence of AIDS-defining opportunistic infections like cytomegalovirus, *P. jiroveci* and *Mycobacterium*-intracellular.[1] Classical risk factors associated with DVT like immobility, cigarette smoking, advanced age, pregnancy, pelvic surgery and personal or family history of DVT may or may not be present in HIV-infected patient presenting with DVT.[1,3,4]

In our case, HIV-infected soldier is 38 years old with no classical risk factors present for the development of DVT. He was on HAART, which included zidovudine, lamivudine and nevirapine with cotrimoxazole prophylaxis. He did not have any AIDS defining opportunistic infections such as cytologmegalovirus, *Mycobacterium* avium complex, or *Pneumocystis jerovecii* infection. There was a definite period of hospitalization of 4 weeks prior to his developing of DVT left lower limb. He visit OPD with chief complain of fever and loose motion from last 2 weeks duration prior to hospitalization and was clinically diagnosed to have an enteric fever.

Salmonella bacteremia is a known opportunistic infection in HIV-infected patient and India we have a high prevalence of *S. typhi* infection but due to lack of reports association between incidences of two infections are poorly determined.[13-17] However, a study in Peru has found typhoid fever to be 60 times

more common in HIV-infected patients than in the general population.[7] *S. typhi* infections can cause life-threatening complications in HIV/AIDS patients[18] and there are case reports to find large vessel thrombosis involving femoral artery.[19] Laboratory diagnosis of enteric fever is made by cultures of blood, stool, urine, and bone marrow with sensitivity of 55-75%, 40-55%, 5-23%, and 85-95%, respectively.[20-22] These bacterial culture activity is limited in endemic developing countries like India and so WIDAL serodiagnostic test is widely used[23] that detects antibody to O and H antigen of *S. typhi*.[24] Studies have shown that a single high titer of >1:320 of O antibody in serum is highly suggestive of enteric fever with sensitivity of 74% in clinically identified patients. IgM/IgG antibody to *S. typhi* lipopolysaccharide antigen has been developed to diagnose enteric fever, but it cannot differentiate between *S. typhi* and *Salmonella* paratyphi C infection.[23]

In our case, the HIV-positive individual was clinically found to have an enteric fever and laboratory test suggestive of the condition was WIDAL seropositive of high titer >1:320 of O antibody and IgM typhoid test positive. Due to inadequate infrastructure, cultures could not be done. He was found to have immunological failure as his CD4 count during hospitalization was 172 cells/cumm (had CD4 count of 333 cells/cumm 3 months back) due to adherence to prescribed HAART<95% for 3 months which resulted in clinical failure (WHO clinical stage3). He was treated empirically for enteric fever with ceftriaxone and his first line HAART was continued given poor adherence to HAART along with opportunistic infection prophylaxis. His response to the therapy was satisfactory but 1 week after developed swelling and pain of left lower limb, diagnosed as DVT of left lower extremity common femoral, superficial femoral, popliteal and common iliac veins based on Doppler USG studies of left lower limb which was is in keeping with the previous reports that the most characteristic anatomical location of DVT in HIV-infected patients is the lower extremity.[25]

We attribute this development of DVT in our case to be multifactorial like HIV infection perse1,3,4,12, hospitalization as an attributable risk factor1, low CD4 count (<200 cells/cumm),[26] infection (enteric fever).[10] Our patients responded adequately to standard therapy for DVT along with the continuation of HAART.

## CONCLUSION

The incidence of DVT in HIV/AIDS is 10 times greater than the standard population.[12] Recent Infection or inflammation has a strong association with the development of thrombosis in HIV-positive patients who can have absent classical predisposing factors of DVT. Physicians involved in the care of HIV-positive patients should be aware of this condition and the associated aggravating risk factors in them so as to provide timely management.

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