Deep Venous Thrombosis in HIV Infected Patients: Case Report and Review

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Abstract: *Human immunodeficiency virus (HIV) is known to be associated with venous thromboembolism (VTE). Africa is the continent most affected by HIV. However, few studies on VTE affecting HIV subjects have been carried in this area. Here, we report the case of a 38-year-old HIV positive woman,admitted for non-febrile enteritis. She was non-compliant to highly active antiretroviral therapy (HAART) with severe immudépression and high viral replication. Left lower limb deep vein thrombosis (DVT) was diagnosed by Doppler-ultrasound. A multifocal tuberculosis was also diagnosed(confirmed on lymph node, lungs, and probably on spleen and peritoneum). Patient was treated by classical anti-tuberculosis treatment and anticoagulant.This case confirm the increased risk for VTE in in HIV subjects, especially with opportunistic infections.*

Keywords: *Deep venous thrombosis, HIV, immunodepression, Sub-Saharan Africa*

INTRODUCTION

Human Immunodeficiency Virus (HIV) infection is a public health problem worldwide, with a prevalence of 36.7 million people worldwide in 2015, with 70% of global infections in Africa [1]. In Cameroon, its prevalence reaches 4.3 %. It is known as an etiology of venous thromboembolism (VTE), either by itself or by its complications. HIV infection increases the risk of VTE in HIV-positive patients by two to tenfold [2]. Opportunistic infections and the duration of HIV infection play a major role in its occurrence. Few studies are done on VTE in Africa, let alone in the HIV-infected patient yet this condition and its complications are common. These patients with chronic diseases in Cameroon have many difficulties to obtain optimal care. These are of a financial order (these are often patients with long-term HIV status or concomitant conditions that are financially difficult to manage by the patient), drug interactions and adverse drug reactions, and psychological disorders.

Our goal is to draw the attention of caregivers to the systematic research for VTE in HIV-infected patients. Here, we present a case of VTE in a HIV patient incompliant to her treatment with opportunistic infection.

CASE PRESENTATION:

A 38-year-old woman was referred to the emergency department for several episodes of liquid, non-bloody mucous stool without other digestive signs. She is HIV positive, known for 2 years. She is non-observant to her treatment with tenofovir-lamivudine-nevirapine. The physical examination on admission revealed hypotension (BP 70/50 mmHg) with pulse at 79 bpm, polypnea at 26 cycles/min and hypothermia at 35.5°c**.** We found an inflammatory left lower limb we found an inflammatory left lower limb, pain on the palpation of the calf, Homans's sign was present and slouching of the calf was reduced, pain on the palpation of the calf, Homans's sign was present and slouching of the calf was reduced. The Wells's score was estimated at 4. In addition, there were ascites without evidence of portal hypertension, multiple non-inflammatory cervical adenopathies, In addition, there were ascites without evidence of portal hypertension, multiple non-inflammatory cervical adenopathies, coarse crackles at the right lung base and an anemic syndrome.

The laboratory tests performed found severe hypochromic microcytic anemia at 6.6 g/dl, moderate hyponatremia at 127.8 mmol/l. Parasitic coprology and the search for opportunistic germs were negative. The analysis of the ascites fluid found lymphocytic exudate. The CD4 cells count was 18 cells / mm³ and the HIV viral load was 1438425 copies/ml (6.2 logs/ ml). PT, BUN, serum creatinine, and transaminases were normal. Mycobacterium tuberculosis was identified by PCR (Gen X-pert®) on the lymph node biopsy fragments. It was sensitive to rifampicin. Pathology of the lymph node biopsy fragments found caseous necrosis. The chest X-ray found micronodular opacities in both lung fields with positive acid-fast bacillary at

the sputum test. Abdominal ultrasound revealed ascites of moderate abundance, bilateral coeliomesenteric, bilateral iliac adenopathies, and a heteronodular spleen with centimetric hypoechogenic nodules. Venous Doppler ultrasound to of the lower limbs found a left popliteal vein thrombosis extending to the common iliac vein (Figure 1). We concluded in multifocal tuberculosis (pulmonary, lymph nodes, splenic and peritoneal) associated extensive LLL DVT in a severely immunocompromised HIV patient with failure of first-line antiretroviral therapy.

The patient was treated with antituberculosis drugs (combination Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide), anticoagulant (Rivaroxaban), water restriction and we modified her antiretroviral treatment in favor of Tenofovir-lamivudine-Efavirenz given the interactions between the nevirapine and rifampicin. Chemoprophylaxis with cotrimoxazole was continued. The patient was discharged on the 24th day of hospitalization.

DISCUSSION

Various studies on VTE in HIV positive patients have been carried out [3–5]. They revealed that the epidemiological data of the HIV patient are different from those of the general population.

The incidence of VTE is 0.1% per year in the general population. It increases with age [6]. This is different in the HIV population; it is two to ten times higher compared to the rest of the population and is even higher in the HIV patient taking intravenous drugs and in AIDS patients [7,8]. Complications due to tumors, especially, Kaposi's sarcoma would promote the risk of developing VTE. The incidence of VTE has probably been underestimated because the data collected are hospital-based and asymptomatic patients were not evaluated [8]. Studies in Africa have found a prevalence of VTE in HIV-immunocompromised subjects at 10.2% [9]. This prevalence reached 42.8% in Abidjan, 45% in Ouagadougou and 51.8% in South Africa [10–12]. In Cameroon, two studies have been conducted on VTE seeking HIV as a risk factor. They respectively found a prevalence of 11.1% and 19.1% [13,14].

The age of onset of VTE in HIV positive patients is earlier compared to the rest of the population. In most studies, it is close to 40 years, thus 20 years younger than non-HIV-infected patients [3,4]. It has been assumed that HIV infection causes premature cell aging, which would continue even years after viral suppression, which would explain why well-controlled patients may have thromboembolic events [15].

In contrast to the general population where there is no predominance of one gender over the other, in HIV-infected patients, however, not significant, we noted a male predominance. Classic risk factors of VTE identified in Africa are prolonged bed rest, recurrent

VTE. Less obesity and obstetric causes are encountered [9]. The risk factors associated with the occurrence of VTE in HIV patients identified by Sullivan are age greater than 45 years, hospitalization, presence of opportunistic disease (Cytomegalovirus, pneumocystosis, tuberculosis), and use of Indinavir (protease inhibitor) [5]. Others found severe immunosuppression to HIV (CD4 <200 cells / mm^3), drug injection use and the presence of HIV-associated neoplasia including Kaposi's sarcoma [7,16].

The **pathophysiology** of VTE during HIV infection is not fully understood. It should be based like that of immunocompetent patients, on the Virchow triad.

Venous stasis

It could be the result of bed rest observed during opportunistic pathologies sometimes motivating hospitalization. This is why it was one of the risk factors MVTE found by Sullivan[5].

The hypercoagulability

It is common in immunocompromised patients and linked to an imbalance of the hemostatic balance in favor of thrombotic manifestations has been observed in patients infected with HIV. This occurs at multiple levels.

- Protein S deficiency

Protein S deficiency (PS) is the most important factor of thrombophilia found in HIV. It is usually a type III deficiency (decreased levels of free S protein with normal levels of total S protein) [2,17]. In HIV-infected patients, its prevalence varies between 27 and 78 %, and it results in thromboembolic disease in 12% of cases [2,18].

In patients with type III deficiency, the etiology could be multifactorial, related to anti-PS antibodies, antiphospholipid antibodies [19], tumor necrosis factor-alpha (TNF-α) and opportunistic infections[2,18].

- Protein C deficiency

In seropositive patients, protein C deficiency (PC) correlates with the level of immunodepression [2,20]. PC level is reduced in opportunistic infections and their treatment is correcting it [2,17].

- Antithrombin deficiency

Antithrombin deficiency (AT) has been reported in HIV-infected patients, but there does not appear to be a relationship between HIV infection and AT deficiency [2,3]. The etiologies of this deficiency could be related to a urinary leakage of AT during a nephrotic syndrome, a digestive leakage during enteropathies, a lack of synthesis in case of malnutrition or liver diseases.

- Anti-phospholipid antibodies

Many autoantibodies are produced during HIV infection, the most common being those against cardiolipin (anti-cardiolipin antibody or aCL) and lupus anticoagulants (LA) [21]. The frequency of these antibodies differs according to the studies and the type of antibody sought. The aCL are present in 86% of patients studied [22]. LA was found in 44% of AIDS patients [21]. Anti-β2 GPIs were positive in only 3.4% with no difference in non-HIV-infected patients [23].

The clinical translation of this elevation remains controversial according to the studies (associated in some studies with an ischemic stroke thrombotic risk, cutaneous necrosis or testicular thrombosis, while for others, antibodies aPL were not accompanied by a higher thrombotic risk in HIV-positive patients) [2].

- Hyperhomocysteinemia

It is considered an independent marker of arterial and venous vascular risk [24]. The Kang classification defines three levels of hyperhomocysteinemia: moderate (15 to 30 μmol/l), intermediate (30 to 100 μmol / l), severe (> 100 μmol / l).

Hyperhomocysteinemia has been reported in 8.7-28.3% of HIV-infected patients [25,26]. However, it would be unrelated to the stage of infection, viral load, ARV treatment or CD4 cell counts. On the other hand, a significant link with cardiovascular risk was noted [25].

- The Von Willebrand Factor

This factor is synthesized by the endothelial cells and the cells of the megakaryocytic line. Its plasma level is frequently high in HIV-infected individuals. This increase whose mechanism is not well known seems to be correlated with the stage of evolution of the disease [27].

- The concentration of factor VIII

The increased plasmatic concentration of factor VIII rises the risk of thromboembolic events. Its elevation during HIV infection has been reported by several authors with a significant downward correlation of CD4 cell counts [28,29].

Others factors molecular factors associated with HIV includes the second heparin cofactor deficiency and fibrinolytic system abnormalities have been described [18,30].

- Inflammation during HIV

Patients infected with HIV have chronic inflammation. This is responsible for the activation of the hemostatic system [31]. In HIV-positive patients, the mechanisms identified are as follows:cytokines such as tumor necrosis factor (TNFα), interleukin-1 (IL1), and interleukin-6 (IL6) activate the clotting pathway and can also lower the expression of many proteins necessary for fibrinolysis; Inflammation can also lead

to a decrease in functional protein S by increasing the level of C4bBP, and thus the transformation of the free form of PS to the bound form [28].

Endothelial dysfunction

The hypothesis of endothelial dysfunction as etiology of VTE in HIV-infected patients was evoked. This is based on indirect arguments such as the elevation of PS and VWF that are synthesized by the endothelium, and whose rates increase in case of endothelial injury. This hypothesis was confirmed by the measurement of vascular dilation mediated by the vascular flow. It was lowered in HIV-infected patients and intravenous drug users, high viral load and alcoholism [32,33].

HIV itself is responsible for endothelial dysfunction, through the tat protein (this is responsible for an increase in the expression of adhesion molecules, stimulation of endothelial growth, platelet activation and the creation of free radicals) and a reduction in circulating levels of nitric oxide (NO) and prostacyclin [2,34,35]. Figure 3 summarizes the pathophysiology of VTE during HIV infection.

The **diagnosis** of VTE in HIV-infected patients rests on the same basis as that of the non-HIV-infected patient: clinical suspicion, then paraclinical confirmation.

The diagnosis of VTE in HIV-infected patients may be difficult because of its clinical presentation that can simulate opportunistic conditions (pulmonary embolism confused to respiratory disease). Its classic expression is the same as in the uninfected, affecting in order of frequency, the popliteal veins, femoral and pulmonary arteries. The clinical presentation, however, differs, by abdominal involvement (portal and splenic), the high incidence of recurrence and the occurrence of extensive thrombosis [2].

The **management** of VTE in the HIV-infected patient is similar to that of the uninfected patient. However, in these patients attention needs to be focused on three points:

- Prevention: the VTE occurs mainly in a patient with opportunistic conditions, any patient with an opportunistic condition must be subject, much more than others to a VTE screening. Treatment of opportunistic conditions appears to reduce the incidence of VTE [3];

- Curative treatment: Few HIV-infected patients are in treatment intervals during VKA therapy (34.5%) [36]. The HIV-infected patient is at risk for drug interactions including VKA and ARV, VKA and Antituberculosis drugs (rifampicin), DAOC and azole antifungals (used for the treatment of histoplasmosis).

CONCLUSION

VTE is not uncommon in HIV immunocompromised patients. Its occurrence is multifactorial, favored in our African context by the persistence of a significant

viremia and opportunistic infections. The patients are mostly young and the clinical presentation is sometimes atypical. There is, therefore, a need for better screening and prevention in the immuno compromised person with HIV.

Authors' Contributions

All the authors made a major contribution to the patient's clinical care and the intellectual content of this manuscript.

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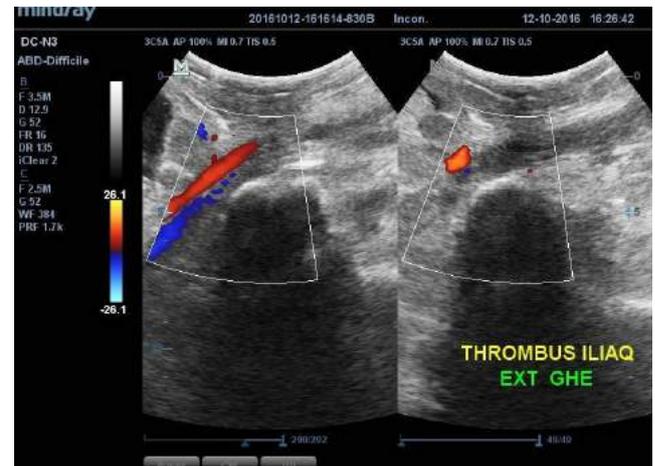
TABLES AND FIGURES

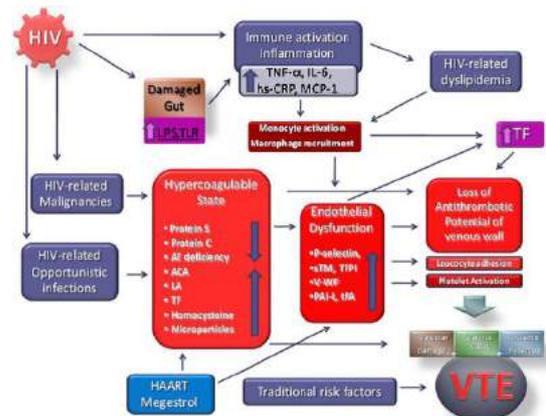**Figure 1:** *Left external iliac vein thrombosis*

Figure 2: *Diagram of the pathophysiology of VTE in HIV-infected patients[2]*