Case Report

PORTAL VEIN THROMBOSIS IN A PATIENT WITH HIV TREATED WITH A PROTEASE INHIBITOR-CONTAINING REGIMEN

P. Soentjens¹, B. Ostyn², S. Van Outryve³, D. Ysebaert⁴, M. Vekemans², R. Colebunders²

Key words: portal vein thrombosis, protein S deficiency, hyperhomocysteinemia, von Willebrand antigen, factor VIII, human immunodeficiency virus, splenorenal shunt, highly active antiretroviral therapy

ABSTRACT

We report a case of an HIV seropositive female patient treated with a protease inhibitor-containing regimen who developed recurrent severe life-threatening episodes of haematemesis over time, caused by ruptured oesophageal varices as a consequence of a portal vein thrombosis. Coagulation tests revealed a protein S deficiency, an elevated homocysteinemia and a constitutional elevated plasma factor VIII coagulant activity. These coagulopathies and the HIV infection are independent risk factors for developing venous thromboembolic events. The protease inhibitor treatment may have played a role in increasing the thromboembolic risk. The recurrent bleedings only stopped after invasive surgery. The invasive splenorenal shunt operation was in this case a life-saving procedure.

INTRODUCTION

Venous thrombembolism (VTE) is reported 10 times more in patients with HIV infection compared with a general population of a comparative age group (1). The incidence of VTE is 2.6 per 1000 person-years in HIV patients (2). Autopsy studies reveal high rates of previously undiagnosed thromboembolism among patients with AIDS (3).

Thrombosis manifests itself as a multicausal disease. HIV-associated thrombosis occurs likely in the absence of common thrombophilic risk factors, such as advanced age, immobility, smoking, family or personal history of deep venous thrombosis, recent surgical intervention or traumatic event, pregnancy or recent oestrogen hormone therapy (4).

HIV is an independent risk factor for VTE, influencing coagulation factors, endothelial dysfunction, platelet activation and inflammatory parameters (4-5). HIV is also related to opportunistic infections, to myeloproliferative, to neoplastic and to hepatic disorders which all predispose to VTE (4).
Portal vein thrombosis (PVT) has been rarely described in persons with HIV infection. To our knowledge, only 10 case reports of PVT and HIV infection have been published (Table 1) (6-11).

We report a case of a female patient with HIV infection treated with a protease inhibitor (PI) -containing regimen who presented with recurrent life-threatening episodes of haematemesis caused by ruptured oesophageal varices as a consequence of a PVT.

Table 1: Reported patients with HIV-infection and portal vein thrombosis (PVT)

<table>
<thead>
<tr>
<th>PATIENT CHARACTERISTICS</th>
<th>Reference</th>
<th>Gender</th>
<th>HIV type</th>
<th>CD4 nadir (µl)</th>
<th>CD4 at the moment of the PVT (µl)</th>
<th>Duration of HAART*</th>
<th>Duration of PI-treatment**</th>
<th>PI at the moment of PVT</th>
<th>Lipodystrophy</th>
<th>Splenomegaly</th>
<th>Variceal bleeding</th>
<th>Ascites</th>
<th>Liver biopsy</th>
<th>Coagulation deficiencies</th>
<th>Elevated coagulation factors</th>
<th>Our patient</th>
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<tr>
<td></td>
<td>6</td>
<td>male</td>
<td>1</td>
<td>124</td>
<td>280</td>
<td>8 m</td>
<td>no PI</td>
<td>no</td>
<td>no</td>
<td>yes</td>
<td>no</td>
<td>no</td>
<td>NP</td>
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<td>anti-cardiolpin antibodies</td>
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<td></td>
<td></td>
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<td>NP</td>
<td>no</td>
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<td></td>
<td></td>
<td>yes</td>
<td>no</td>
<td>yes</td>
<td>NP</td>
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<td>factor VIII : C von Willebrand factor homocysteine</td>
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<td>no</td>
<td>NP</td>
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<td>splenorenal shunt</td>
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<td>no</td>
<td>yes</td>
<td>NM</td>
<td>no</td>
<td>splenorenal shunt</td>
<td></td>
</tr>
</tbody>
</table>

THERAPEUTIC INTERVENTIONS

| Pi-treatment stopped | no | NM | yes | yes | yes | NM | NM | no PI | NM | yes | yes |
| Anticoagulant        | no | NM | yes | no  | no  | no | yes | NM    | NM | NM | yes |
| Shunting             | no | NM | yes | no  | no  | no | no  | no    | TIPS *** | no | splenorenal shunt |

OUTCOME

| Recurrence of bleeding | NM | yes | no  | no  | NM | NM | no  | no  | NM | no  | no  |
| Resolution of the PVT  | caverno | no  | yes | yes | NM | no  | no  | no  | NM | no  | yes |

NM = not mentioned; NP = not performed; m = month; y = year; rit = ritonavir, saq = saquinavir; ind = indinavir; lop = lopinavir.

*HAART: highly active antiretroviral treatment
**PI: protease inhibitor
***TIPS: transjugular intrahepatic portosystemic shunt stenting

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CASE REPORT

A 38-year-old African woman with HIV infection was admitted to the hospital with severe haematemesis, melena and hypotension. She had been treated with multiple highly active antiretroviral treatment (HAART) regimens, including several PI’s (ritonavir, indinavir, nelfinavir, saquinavir and amprenavir) since 1997. Treatment regimens had been changed several times because of non-adherence and side effects.

On admission her treatment regimen consisted of abacavir (300 mg BD), stavudine (30 mg BD) and lopinavir/ritonavir (400/100 mg BD). She had also been receiving cabergoline since October 1997 for a microprolactinoma.

She presented with signs of pronounced lipodystrophy. Her abdomen was diffusely tender over the epigastrium and hepatosplenomegaly was suspected clinically.

Laboratory examinations showed a hypochromic anaemia (haemoglobin 8.8 g/dl (normal values (N): 12-15 g/dl)), a white blood cell count of 4.100 cells/mm³ (N: 4.3-10.10³ cells/mm³) and thrombocytes of 66 /mm³ (N: 140-440 /mm³). Several liver tests were abnormal: alkaline phosphatase 256 IU/I (N: 36-95 IU/I); aspartate aminotransferase 87 IU/I (N: 5-40 IU/I); alanine aminotrans- ferase 56 IU/I (N: 7-56 IU/I); gamma-glutamylpeptidase 207 IU/I (N: 11-29 IU/I); lactate dehydrogenase 792 IU/I (N: 313-618 IU/I) and albumin 2.5 g/dl (N: 3.5-5.2 g/dl). Her CD4⁺ lymphocyte count was 249 cells/mm³ and her viral load was 5590 copies/ml.

Upper gastrointestinal endoscopy upon admission revealed grade II oesophageal varices with active bleeding, requiring of insertion of three ligatures. After initial stabilisation of the patient’s clinical condition a Doppler ultrasonography and a CT scan of the abdomen were performed. Portal vein thrombosis, splenomegaly and a small amount of ascites fluid were discovered. A liver biopsy revealed some signs of aspecific inflammation, but no signs of hepatitis, cirrhosis or steatosis.

Acquired risk factors for thrombo-embolism, such as smoking, a family or personal history of deep venous thrombosis (DVT), a recent surgical intervention or traumatic event, pregnancy or recent oestrogen hormone therapy were absent.

After exclusion of hepatic, neoplastic, myeloproliferative disorders and opportunistic infections, a detailed coagulation study was performed. The results were compatible with protein S (PS) deficiency: total PS antigen, free PS antigen and PS activity values were 41% (N: 66-204%), 36% (N: 46-204%) and 18% (N: 60-150%), respectively. Elevated levels of factor VIII: C 312 % (N: 60-150%), von Willebrand factor 266 % (N: 60-150%) and homocysteinaemia 25 µmol/l (N: <15 µmol/l) were also discovered. Other coagulation parameters, including fibrinogen, antithrombin III, heparin cofactor II, factor V, factor X, protein C, plasminogen, prothrombin and activated partial thromboplastin time, were within normal ranges. Circulating lupus anticoagulant, antinuclear and anticytodiolin antibodies were absent. A molecular investigation could not identify any of the known gene mutations for congenital protein S deficiency.

Initially she was treated with beta-blocking agents, to reduce her heart rate and treatment with coumarines was prescribed, to inhibit vitamin K dependent clotting factors. Consecutively, vitamin B12 and folate were administered to lower the homocystein level.

Several months later she was readmitted to the intensive care unit, because of a second episode of variceal bleeding and hypotension. Multiple sessions of ligatures and full beta-blockade with a heart rate of 50-60/min, could not stop the recurrent active variceal bleedings. Finally, a selective Warren distal splenorenal shunt operation was carried out. Subsequently, the oesophageal varices regressed. A control Doppler ultrasonography of the abdomen revealed a normal liver, a portal thrombosis with a heterogenous flow, an open splenorenal shunt and splenomegaly. On discharge, her antiviral treatment was switched to a regimen without a PI: didanosine (250 mg QD), abacavir (300 mg BD) and efavirenz (600 mg QD) and her anticoagulation was continued. Later the efavirenz was stopped and zidovudine, lamivudine and tenofovir were added. There has been no recurrence of bleeding for more than three years. Repetitive coagulation studies without coumarines showed similar results: a persistent protein S deficiency of 40% (N: 66-204%) and an elevated factor VIII coagulants of 410% (N: 60-150%).

DISCUSSION

The classic clinical course of patients with PVT is characterised by repeated bouts of variceal haemorrhage, with an average of 2.5 of 5 episodes per patient (12). Approximately 10 to 20 % of patients with PVT develop spontaneous splenoadrenalorenal or splenogastrorenal shunts, which decrease the frequency of bleeding episodes (12).

The mortality from bleeding secondary to variceal haemorrhage in PVT in patients without cirrhosis is approximately 5% (12).
Multiple risk factors are a prerequisite for thrombosis to develop. Common acquired risk factors for thromboembolism (4), were absent in our patient. Acute opportunistic infections and malignancy were also excluded. HIV infection and several changed coagulation and endothelial factors, like PS deficiency, hyperhomocysteinemia, elevated level of plasma factor VIII:C and elevated level of von Willebrand factor (vWF), may have played an important role in causing the PVT in our case. Finally, treatment with PIs and related lipodystrophy can predispose for VTE.

HIV is an independent risk factor for VTE (13). HIV patients tend to develop VTE at a younger age compared with the general population (10, 12, 13).

HIV infection may also contribute to a hypercoagulable state due to an elevated risk of specific complications such as opportunistic infections and malignancies (14). In a regression model the odds ratio for thrombosis increased to 1.5 for patients with an AIDS-defining opportunistic infection (2). In the era of HAART, patients are characterized at the time of thrombosis by an advanced CDC HIV Classification (and/or low nadir CD4+ lymphocyte count) but not by a low CD4+ lymphocyte count or an elevated HIV load at presentation (10). Our patient was 38 years old, had no AIDS-defining diseases in the past and had a nadir CD4+ lymphocyte count of 18 cells/mm³. Her CD4+ lymphocyte count at presentation of the PVT was 249 cells/mm³ and her viral load was 5590 copies/ml.

Another reason for the HIV-related hypercoagulability is that aspartyl proteases, like cathepsin D, angiotensin II, renin and endothelin are involved in the regulation of coagulation, and HIV itself contains also an aspartyl protease that interferes in this thrombotic cascade (8, 15-16).

HIV can also damage endothelial cells, and levels of endothelial activation markers (vWF, VCAM-1, sICAM-1) may be elevated. Endothelial cell perturbation is more present in HIV infection and may be related to higher viral loads and more advanced diseases (17). Levels of coagulation markers (e.g. d-dimers and thrombin-antithrombin III-complexes) and platelet activation may also be increased in people with HIV infection, but to a lesser extent than the endothelial markers (18-19). In our case the levels of vWF were elevated.

HIV is associated with the presence of antiphospholipid antibodies and lupus anticoagulant and also with decreased levels of PS and protein C and antithrombin III (20-24). In our patient PS deficiency was diagnosed together with hyperhomocysteinaemia and a persistent high level of factor VIII, who are also associated with VTE (25-31). Some data suggest that PS deficiency is not correlated with HIV disease severity (32), although more recent studies showed that PS deficiency develops in patients with HIV and acute illness and that this deficiency may be reversible after treatment of the opportunistic infections (33). One of the mechanisms of decreased PS levels in HIV is possibly due to the presence of specific autoantibodies (34).

Recent epidemiological studies emphasize the increased incidence of VTE, including myocardial infarction, in HIV patients after the introduction of HAART. Some researchers are suggesting that clinically detected thrombosis is more common in HIV-infected individuals for whom PIs (in particular indinavir) have been prescribed (2). Several cases of thrombosis associated with PI-containing regimens have been reported (6-10, 35). VTE occurs following initiation of different PIs, like saquinavir, ritonavir, indinavir and nelfinavir, so that a PI class-effect would be most likely the cause of these syndromes. The importance of PI-based therapy in promoting thrombosis through pleiotropic effects, including alterations in lipid, plasminogen activator inhibitor-1, TNF-α and fibrogen levels, is uncertain. TNF-α and plasminogen activator inhibitor-1 levels are elevated in patients taking PIs, suggesting a possible PI-associated deficiency in the cascade of fibrinolysis (36). PIs have been linked to thrombosis, especially in the context of PI-related toxicity, including fat redistribution, dyslipidaemia and insulin resistance (named lipodystrophic syndrome). Despite the apparent decrease in endothelial perturbation, the patients on PIs who develop lipodystrophy have increased levels of sVCAM-1 and vWF and increased levels of endothelial injury marker (soluble thrombomodulin), which turn them into a high atherothrombotic risk group (37). It has also been suggested that PIs could interfere with the hepatic regulation of thrombotic proteins, leading to a prothrombotic state. It is clear that the role of PIs in modulating this thrombotic cascade remains to be determined. In our lipodystrophic patient, who received several PI regimens (ritonavir, indinavir, nelfinavir, saquinavir and amprenavir) since 1997 and who was on lopinavir / ritonavir, when she developed the PVT, a PI-sparing regimen was prescribed in an attempt to reduce lipodystrophy and related metabolic disorders.

Endoscopic variceal sclerotherapy (EVS) should be attempted in patients with PVT as the first line of treatment to prevent bleeding, given the high success, the low mortality, and tolerable morbidity of this procedure. Patients may require several sessions in order to eradicate the varices (12).
Shunt surgery is indicated in patients who continue to bleed despite several EVS procedures, given the risks in shunt surgery of operative death or of hepatic encephalopathy. Several authors report success rates in excess of 80% and rebleeding rates as low as 4% with shunt procedures (12). A selective Warren distal splenorenal shunt operation was carried out successfully in our patient, who had continued to bleed (after several EVS procedures) in order to preserve enough blood flow to the liver (to prevent hepatic encephalopathy) and to divert blood flow away from the gastro-oesophageal junction (to prevent new variceal bleeding).

CONCLUSION

HAART has considerably improved the life expectancy of persons with HIV infection. Antivirals, however, may also cause life-threatening complications (38) such as lactic acidosis, pancreatitis, hypersensitivity reactions, liver toxicity and they may trigger a hypercoagulable state leading to dangerous venous and arterial thrombosis (39).

The improved life expectancy of persons with HIV infection means that medical complications in these patients should increasingly be treated in a similar aggressive way to those of non-HIV-infected individuals. In the case of our patient the splenorenal shunt operation saved her life.

ACKNOWLEDGEMENT

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ABSTRACT

Wij beschrijven een HIV positieve vrouw die onder protease inhibitoren verschillende ernstige levensbedreigende episodes doormaakte van hematemesijs. Een veneuze trombose van de vena portae en een gestageerde ruptuur van de oesofageale varices waren hiervan de oorzaak. Bloedstollingtesten toonden een proteine S deficiëntie, een gestageerde homocysteenemie en een blijvende verhoogde plasma factor VIII activiteit. Deze stollingsstoornissen samen met de HIV infectie zijn onafhankelijke risicofactoren voor diepe veneuze trombose. De behandeling met protease-inhibitoren zou een rol kunnen gespeeld hebben in het veroorzaken van een verhoogde stollingsneiging. De oesofageale bloedingen stopten uiteindelijk na een splenorenale shunt operatie. Deze ingreep was levensreddend.

REFERENCES

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