CASE REPORT

Diagnostic dilemma of coagulation problems in an HIV-positive patient with end-stage liver disease undergoing liver transplantation

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Abstract

Human immunodeficiency virus (HIV) may result in devastating multi-organ complications, including cirrhosis. Consequently, liver transplantation is often required for these patients. We report a case of a 43-year-old female with cryptogenic cirrhosis and HIV on highly active antiretroviral therapy, presenting for non-related living donor liver transplantation. The intra-operative course was complicated by hepatic artery and portal vein thrombosis, requiring thrombectomy. On postoperative day-3, the patient required re-transplantation with a cadaveric donor organ due to primary graft failure.

Key words: Hypercoagulation; Liver transplant; Highly active antiretroviral therapy; Human immunodeficiency virus

Core tip: Liver transplantation is a technically complicated procedure associated with both predictable and unpredictable coagulation abnormalities. The surgeons are more concerned about bleeding than thrombotic complications in cirrhotic patients undergoing liver transplant, but the reality these patients are equally at risk of both complications. The risk of a thrombotic event is even higher in human immunodeficiency virus (HIV) patients on highly active antiretroviral therapy (HAART) both during and after the surgical procedure. This fact should be ranked high in the differential diagnosis of liver allograft failure in liver transplant recipients who are HIV positive and receiving HAART.

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INTRODUCTION

Human immunodeficiency virus (HIV) is a devastating illness with an estimated incidence of 40000 annual cases in the United States. Treatment with highly active antiretroviral therapy (HAART) has allowed for significant immunologic recovery, resulting in a notable decrease in opportunistic infections and prolonged life expectancy. However, treatment with HAART has resulted in the emergence of other complications such as severe hepatotoxicity. We present a case involving a patient with cryptogenic liver disease and HIV whose liver transplantation was complicated by unanticipated hepatic artery and portal vein thrombosis as well as subsequent graft failure.

CASE REPORT

A 43-year-old female with cryptogenic cirrhosis, presented for non-related living donor liver transplantation. Her medical history was notable for HIV, diagnosed in 1994, and HIV-related complications including pneumocystis carinii pneumonia and malabsorption syndrome. Her Model for End-Stage Liver Disease score on the date of the transplant was 24 and her pre-transplant laboratory test results were as follows: serum bilirubin 3.5 mg/dL, INR 1.4, platelet count 70000, and hemoglobin 11 gm/dL; acid-base and electrolytes were within normal range. Due to malabsorption and severe emaciation, she was put on total parenteral nutrition (TPN) was initiated in 2006 and resulted in significant weight gain. Preoperative viral load was undetectable and CD4 count was acceptable at 204/μL. Antiviral therapy included efavirenz (sustiva), a non-nucleoside reverse transcriptase inhibitor, and zidovudine and lamivudine (3TC), which are both nucleoside reverse transcriptase inhibitors. The patient underwent non-related living donor liver transplantation using a right lobe graft donated by a friend. The patient had the standard of care invasive monitoring which include, 2 arterial lines (one radial and one femoral), pulmonary artery catheter, and 18 FG cannula for veno-venous bypass both were established in the right internal jugular vein while another 9 FG cannula was inserted in the left internal jugular and connected to electrical-powered rapid infuser to be available in case of requirement for massive transfusion. As standard of care at our Institution TEE probe was used for continuous cardiac monitoring. All lines were established after induction of general anesthesia and performed by senior anesthesiologist without any complications. As a standard of care for liver transplant recipients, arterial blood gas and thromboelastograph tracing are tested on hourly basis or as the clinical situation demands.

The case progressed smoothly until completion of the vascular anastomosis, when thrombosis of the hepatic artery and portal vein was noticed. The diagnosis of vascular thrombosis was confirmed by Doppler ultrasound monitor. Immediate thrombectomy and heparin treatment was initiated to allow adequate graft perfusion. The thromboelastograph tracing revealed a hypercoagulable state throughout the majority of the case. The only blood products she had received were three units of red blood cells.

On post-operative day 2 (POD 2), the patient's condition deteriorated, with significant elevations in ammonia levels and liver enzymes. Doppler ultrasound examination demonstrated no blood flow through the main vessels. Graft biopsy revealed a submassive ischemic hepatic necrosis, portal vein and hepatic artery branch thrombosis, and non-occlusive hepatic vein thrombosis. Patient was re-listed as a "category 1" for orthotropic liver transplantation (OLT). Although she developed primary graft failure with a clinical picture similar to fulminant hepatic failure, her coagulation profile by TEG remained hypercaogulable and she was kept on heparin infusion during POD 1 and no fresh frozen plasma or platelets were given. A cadaveric organ became available on POD 3. The re-transplantation was completed in less than 8 h without complication during which the patient was placed on continuous IV prostacycline infusion prophylactically to prevent intravascular thrombosis. Her TEG during the second OLT was within normal range and she did not receive any coagulation products until stage III (the neohepatic phase). Postoperatively, the patient's course was complicated with deep vein thrombosis and a new piece of the patient' past medical history that emerged: a questionable hypercoagulable syndrome with possible heparin-induced thrombocytopenia (HIT) that was considered the cause of the problem.

Heparin was discontinued secondary to continuous suspicion for HIT type II and patient was anticoagulated with bivalirudin after her second OLT. The HIT panel and PF4 antibody testing were performed on POD 1 of her first transplant and became available on POD 7, which revealed negative HIT antibody, methylenetetrahydrofolate reductase gene mutation, and factor V leiden mutation with a negative lupus anticoagulant test. After five weeks in the ICU and nine weeks in the hospital, she was discharged for inpatient rehabilitation facility in stable condition.

DISCUSSION

The patient's complicated course raised questions regarding the etiology of the unexpected thrombotic events. The primary concern was heparin-induced thrombocytopenia or HIT type II, which is an antibody-mediated prothrombotic thrombocytopenia. While HIT

type 1 is a non-immune reaction, characterized by self-resolved thrombocytopenia even with continued heparin administration, HIT type II is caused by an IgG antibody that recognizes platelet factor 4 (PF4) and heparin. PF4/heparin complexes bind to platelet surfaces, forming HIT-IgG/PF4/heparin[1] that lead to platelet aggregation and vascular endothelial injury. The typical HIT course results in thrombocytopenia within 4-5 d after exposure to heparin, and patient may develop thrombocytopenia within 10 h of heparin re-exposure[1].

The temporal course is uncharacteristic of HIT type II and there was no documentation that our patient had received heparin. However, she did have a pre-existing PICC line for TPN and heparin may have been used to flush the peripherally inserted central catheter (PICC line). It is known that even the smallest amounts of heparin in the form of coated catheters and line flushes can initiate the cascade of HIT type II in susceptible individuals. Early diagnosis of HIT type II is critical, as it may be associated with serious thrombotic complications with high morbidity and mortality rate related to stroke or amputation. In addition to clinical presentation, laboratory tests are useful in the diagnosis of HIT; however, negative results do not always exclude its diagnosis. These tests can be classified as functional assays and immunlogical assays. Functional assays include heparin-induced platelet aggregation and serotonin release assay, with specificity and sensitivities of 40% and 88% respectively[1]. The immunoassays (used at our institution), which measure IgG, IgM, and IgA antibodies that bind PF4 to heparin such as enzyme-linked immunosorbent assay, have an 86% specificity and a 97% sensitivity. Since HIT type II was ruled out due to the timing of thrombosis and the negative HIT panel, HIV and HAART were considered the main etiology of thrombosis and thrombocytopenia. Primary HIV associated thrombocytopenia is commonly seen in 40% of HIV positive individuals during the course of the disease. Thrombocytopenia may occur during any part of the illness with fluctuating severity based upon the levels of immunosuppression. Other causes of thrombocytopenia in this patient population include opportunistic infections and malignancy[2]. HIV related thrombosis is ten times more common in HIV positive patients than in the general population. The clinical studies reveal that the incidence of venous thromboembolism in HIV positive patients ranges from 0.25%-0.96%, however, this incidence increases to 17% when based on autopsy results[3]. Copur *et al*[4] concluded that the increased frequency of venous thromboembolism in HIV positive individuals is only applicable to those who are ⩽ 50 years of age[4] and our patient age falls in this age bracket. Potential risk factors that place these individuals at higher risk include cytomegalovirus infection, Kaposi sarcoma, intravenous drug use, and medications like erythropoietin, megesterol acetate, and protease inhibitors.

Newly emerging mechanisms continue to emphasize the correlation between antiretroviral therapies and hypercoagulability and antiretroviral therapy may be considered an independent cause of thromboembosis in HIV patients. *In vitro* studies showed that HIV might irritate vascular endothelial cell, thus altering storage and excretion of key proteins such as Von Willebrand factor and antithrombin III and decreased quantities of proteins C and S with possibly of disruption of the fibrinolytic pathway. Pro-inflammatory cytokines which activate the hemostatic system are unregulated during HIV infection and might trigger the coagulation system[5]. In HIV-positive patients and even under well-controlled viral levels, they remain at risk for inflammatory-associated complications such cardiovascular diseases and cancers. It is vital to acknowledge that immune activation results in inflammation and thrombosis, and conversely, inflammation and thrombosis induce immune activation[6]. These cumulative changes may result in a prothrombotic condition, even in well-controlled viral loads as in our patient. Autoantibodies, like lupus anticoagulant may appear in many HIV positive patients (as in our patient), while anticardiolipin antibodies that are associated with the hypercoagulable state have been found in in 45%-50% of HIV positive patients[7]. Interestingly, some of these autoantibodies are higher in HIV-infected women than in HIV-infected, putting women at a higher risk for thrombotic complications[8]. Lijfering *et al*[9] noted a higher risk of venous and arterial thrombosis for those on combinations of antiretroviral therapy, an effect that was amplified for those on protease inhibitor (PI). Possible mechanisms may include PI-induced pleiotropic effects such as alterations in blood lipids with increase in plasminogen activator inhibitor-1 and fibrinogen. It was found that HIV can lead to impairment in vascular endothelial-dependent vasodilatation[10] and may induce dyslipidemia and hyperlipidemia with an increased risk of thrombosis. However, some studies have found that antiviral therapy may be a contributing factor to endothelial dysfunction[11]. No matter which offending agent, the development of vascular endothelial dysfunction will affect all endothelial functions and lead to abnormal vascular relaxation, activation of coagulation, and abnormal immune response. HAART has signi-ficantly improved the outcome and prognosis of HIV patients. However, the potentially serious cardiovascular complications that may be implicated with the use of protease inhibitors cannot be ignored. Still, fear of these complications should not prohibit their use.

In conclusion, liver transplantation is a technically complicated procedure associated with both predictable and unpredictable coagulation abnormalities. In HIV-positive patients on HAART regimens, risk of a thrombotic event is high both during and after any surgical procedure. Thus, prophylactic anticoagulation may be justifiable. During OLT, the administration of

small doses of heparin ($\leqslant$ 3000 units) and frequent monitoring of coagulation by TEG to prevent life-threatening thrombosis should be considered.

COMMENTS

Case characteristics
The authors presented a patient with history of human immunodeficiency virus (HIV) and on highly active antiretroviral therapy (HAART) who underwent orthotropic liver transplantation (OLT) that was complicated by intraoperative thrombosis of the hepatic artery and portal vein. The possible etiologies of the hypercoagulability in this patient were HIV and HAART.

Clinical diagnosis
The hypercoagulability was presented by an immediate intravascular thrombosis and prothrombotic thromboelastograph during the OLT.

Differential diagnosis
The differential diagnosis included: Heparin-induced thrombocytopenia (HIT): Hypercoagulability induced by HIV and HAART and the presence of undiagnosed lupus antibodies.

Laboratory diagnosis
The HIT panel and platelet factor 4 antibody test to exclude the diagnosis of HIT as the etiology for the intravascular thrombosis.

Treatment
Due to ischemic liver graft failure patient was re-transplanted within the 1st 72 h after the diagnosis of primary graft failure.

Related report
Although there are scientific evidences that documented the changes in the coagulation functions in HIV patients, the authors are unaware of such complication in OLT recipient.

Experiences and lessens
It is important when taking care of HIV patients to understand the complicated interaction of the pathological process of the disease itself and the anti-HIV medications. As both the disease and the medications have complicated effects on multiple organ systems such as the effects on the immune and the coagulation systems that can make the clinical presentation quite confusing.

Peer-review
This is an interesting case with a good discussion that this reviewer recommends for to be published only after a series of small issues are fixed.

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