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Significant Hyperfibrinolysis in a Patient With Intracardiac Thrombosis: To Give Antifibrinolytics or Not?

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Abstract. The hemostatic system is a delicate balance between the coagulation, anticoagulation, and fibrinolytic systems and is responsible for preventing both hemorrhage and thrombosis. End stage liver disease is characterized by a rebalanced hemostatic system that is fragile and easily tipped towards either hemorrhage or thrombosis. During an orthotopic liver transplantation, patients are exposed to a wide variety of factors that can shift them from a hypercoagulable state to a hypocoagulable state almost instantaneously. The treatment for these two disease states contradict each other, and therefore patients in this condition can be extremely difficult to manage. Here, we present a patient who underwent an orthotopic liver transplantation and suffered an intracardiac thrombosis shortly after reperfusion of the donor graft, that resolved with supportive care, who then went on to develop severe persistent hyperfibrinolysis and massive hemorrhage that was successfully treated with an antifibrinolytic agent.

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Over the past 2 decades, the old dogma that end-stage liver disease (ESLD) patients are hypocoagulable has been dispelled in favor of the newer concept that coagulation in these patients is rebalanced due to a parallel reduction in both procoagulant and anticoagulant factors.[1] The relative deficiency of both coagulation system drivers makes the balance fragile and it may be tipped toward either hemorrhage or thrombosis, depending on other factors. Fibrinolysis is another complex system that is regulated by both profibrinolytic drivers (eg, tissue plasminogen activator [tPA]) and antifibrinolytic drivers (eg, plasminogen activator inhibitor). Any perturbation of this system may tip the balance toward hyperfibrinolysis, increasing the risk of hemorrhage, or hypofibrinolysis, increasing the risk of thrombosis.

Hemorrhage during orthotopic liver transplantation (OLT) is relatively easy to detect and treat. Thrombosis, however, is frequently unexpected and more difficult to detect before hemodynamic instability occurs. Recent evidence suggests that the occurrence of intracardiac thrombosis (ICT) during OLT is not as rare as was once thought.[2] The majority of cases occur shortly after reperfusion,[2] a period also associated with enhanced fibrinolysis.[3-5] We therefore pose the question of how to treat a patient that suffers both an ICT and significant hyperfibrinolysis? A case of an OLT with a hemodynamically significant ICT and subsequent hyperfibrinolysis with massive blood loss is presented.

CASE DESCRIPTION

A 57-year-old female with a history of ESLD due to hepatitis C s/p OLT (14 years prior) complicated by late hepatic artery thrombosis (HAT) and multiple infected bilomas presented for repeat OLT (MELD-Na 29). Her chronically infected intrahepatic bilomas were well controlled with a percutaneous biliary drain and intravenous (IV) ertapenem and micafungin. She displayed no signs or symptoms of sepsis. Her medical history was otherwise notable for an incidentally discovered right lower lobe pulmonary embolism in the setting of her newly diagnosed HAT. She had a negative hypercoagulability workup and was treated with warfarin, which was reversed with vitamin K before her repeat OLT. Her preoperative laboratories were notable for platelets 92 K/μL, INR 1.6, PTT 36.4 seconds, fibrinogen 413 mg/dL, and a normal thromboelastogram (TEG) except for a mildly elevated alpha angle (α = 76.1 degrees).

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Ethics: The humans involved in this study were treated in a manner in accordance with the Declaration of Helsinki and the Declaration of Istanbul.

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Her preoperative echocardiogram demonstrated an ejection fraction of 65%, no significant valvular disease, and mild pulmonary hypertension (mean pulmonary arterial [PA] pressure 27 mm Hg). Her dobutamine stress echocardiogram was negative for ischemia. The donor graft was from a donation after brain death patient with a post mortem biopsy that showed mild portal fibrosis without significant steatosis.

Anesthesia induction was uneventful. The surgical team then placed a 19-Fr Biomedicus catheter in the femoral vein and a 15-Fr Biomedicus return catheter in the right internal jugular vein. The hepatic dissection was complicated by significant bleeding from dense scar tissue and adhesions despite going on venoveno bypass (VVB). After discussion with the surgeon, no prophylactic heparin was administered before inferior vena cava cross-clamping due to ongoing bleeding. No additional TEG was drawn during the preanhepatic phase; however, conventional coagulation studies were notable for INR, 2.2; PTT, 81.5 seconds; platelets, 43 K/μL, and fibrinogen 95 mg/dL. The hemorrhage and coagulopathy were treated with blood component therapy [10 units of packed red blood cells (pRBC), 4 units of fresh frozen plasma (FFP), 1 unit of platelets, and 10 units of cryoprecipitate] and the use of cell-saver. Improved hemostasis was achieved before completion of the hepatectomy, along with improvement in the conventional coagulation laboratories. The anhepatic phase lasted 81 minutes, during which time the initial coagulopathy had improved (INR, 1.4; PTT, 47.0 seconds; platelets, 62 K/μL; and fibrinogen, 196 mg/dL).

Within 5 minutes of reperfusion, the patient became severely unstable with both systemic and pulmonary systolic blood pressures in the 50s and oxygen saturations in the low 80s. These changes coincided with transesophageal echocardiography (TEE) revealing a large thrombus in the right atrium, a dilated and hypokinetic right ventricle (RV), and an empty left ventricle. A TEG drawn at the time of the ICT remained a flat line for >15 minutes. Supportive care including inotropes, vasopressors, and inhaled nitric oxide was initiated with improvement in RV function, cardiac output, and blood pressure within 15 minutes, and resolution of the clot on TEE within 30 minutes. The patient did not suffer cardiac arrest at any point and did not require chest compressions. Given the rapid improvement in RV function and the resolution of the clot, heparin and tPA were not administered.

Over the next 2 hours, significant nonsurgical bleeding was noted requiring massive transfusion (15 units pRBC, 11 units FFP, 5 units platelets, and 20 units cryoprecipitate). A TEG drawn 40 minutes after reperfusion demonstrated a low maximum amplitude (MA, 40.3 mm) with significant lysis (LY30, 37.6%). Transesophageal echocardiography showed no further ICT with normal biventricular function and PA pressures. The low MA was treated with platelets and cryoprecipitate; however, the hemorrhage did not improve. After considerable discussion, 3 g of ε-aminocaproic acid (EACA) was given for the hyperfibrinolysis. Hemostasis was achieved over the next hour and a repeat TEG demonstrated resolution of the hyperfibrinolysis (LY30 = 0%). The remainder of the case proceeded uneventfully with minimal transfusion and the graft demonstrated good function. The patient was discharged home on postoperative day 16.

DISCUSSION

Intracardiac thrombosis is a major cause of morbidity and mortality in OLT,[2] which contradicts the classical notion that the coagulopathy of ESLD is protective for venous thromboembolism.[6] The incidence has been estimated to range between 1.2% and 6.25%[7,8] with an intraoperative mortality of 30% to 68%.[2,9] There have been multiple suggested risk factors including the use of VVB, antifibrinolytics, and PA catheters[2]; however, all of these are questionable in systematic reviews. A single-center retrospective analysis demonstrated that the prophylactic administration of IV heparin in the presence of hypercoagulability may prevent the development of ICT and is not associated with an increased transfusion requirement[10]; however, a randomized controlled trial is lacking. No definitive data exist yet on how to best manage this complication. Based on current literature and experiences at their institution, Protin et al[11] established an algorithm for the management of ICT during OLT based on the size of the clot and the hemodynamic status of the patient, starting with supportive care and progressing to IV heparin, then low-dose tPA, and finally high-dose tPA with consideration for extracorporeal membrane oxygenation.

Hyperfibrinolysis is another complication that can occur during OLT, most commonly during the anhepatic phase and after reperfusion.[3-5] The incidence of hyperfibrinolysis at 5 minutes postreperfusion is 71% to 84%; however, this hyperfibrinolysis usually resolves spontaneously within 30 to 60 minutes and does not recur.[4,5] If the hyperfibrinolysis persists and leads to increased hemorrhage, the administration of antifibrinolytic agents may be indicated. Although the exact mechanism of the increased fibrinolytic activity during reperfusion is not fully understood, it is attributed to increased tPA levels during the anhepatic phase due to a lack of hepatic clearance and its enhanced release after reperfusion.[3] The use of antifibrinolytics prophylactically to prevent hyperfibrinolysis is a highly debated topic and is beyond the scope of this article; however, concerns raised by case reports[7,12-15] and experts in the field regarding a possible link between antifibrinolytics and thrombosis have shifted practice away from the routine use of antifibrinolytics at many institutions. Two notions seem to be agreed upon by experts: consider antifibrinolytics when hyperfibrinolysis is confirmed on TEG and correlates with clinical bleeding, and prophylactic antifibrinolytics should be avoided in patients at increased risk for thrombotic complications.[16,17]

This patient had multiple proposed risk factors for ICT including a history of pulmonary embolism, a chronic inflammatory state due to her infected bilomas, the use of VVB, significant blood product transfusion, and a high MELD-Na. Prophylactic heparin before inferior vena cava clamping was also not administered due to significant bleeding at that time. Therefore, based on our current understanding, she was likely at a higher risk of developing an ICT during OLT.

This patient presented us with a treatment dichotomy involving both an ICT and significant hyperfibrinolysis. The first decision that needed to be made was how to treat the ICT. It has been suggested that clot lysis typically occurs within 30 minutes without exogenous fibrinolytic therapy as long as cardiac output can be maintained.[7] This notion held true in our case as supportive care was immediately initiated in an attempt to maintain an adequate cardiac output and the clot resolved spontaneously. Given the

rapid resolution of the thrombus and normalization of RV function with improved hemodynamics, no further treatment was warranted.

At 2 hours postreperfusion, our patient had severe persistent nonsurgical bleeding despite improved coagulation studies apart from a TEG showing significant hyperfibrinolysis. The treatment of choice in this setting would usually be an antifibrinolytic. However, this decision was complicated by the patient's history combined with her recent ICT, with the theoretical concern that antifibrinolytic therapy may precipitate a repeat episode of ICT. To our knowledge, no other similar case has been presented in the literature that could have been used to help guide treatment. Molenaar et al[18] performed a meta-analysis of the efficacy and safety of antifibrinolytics in OLT and found that there was no increased risk of HAT, venous thromboembolic events, or perioperative mortality with the use of EACA. However, a lack of differences in thromboembolic events in their study does not necessarily mean that there is no increased thrombotic risk associated with the use of EACA in a specific subset of patients, such as ours. Therefore, we made sure to correct other reasons for her coagulopathy before ultimately deciding that the hyperfibrinolysis was likely the culprit for the persistent hemorrhage. Given the length of time since the ICT had resolved, the current hemodynamic stability of the patient, and the TEE showing no evidence of ICT with normal biventricular function, the decision was made to treat the hyperfibrinolysis and persistent bleeding with 3 g of EACA over 20 minutes. This decision was made with input from all members of the transplant team given the real concern for additional and possible fatal ICT after administration of the drug. Kang et al[19] demonstrated that 1 g of EACA effectively treated all 20 patients undergoing OLT who demonstrated active fibrinolysis, suggesting that a lower dose may have been equally effective. Fortunately, in our patient, the EACA rapidly achieved hemostasis without additional thrombosis.

We do not recommend giving a prophylactic antifibrinolytic in the setting of a hypercoagulable state or when evidence of a thrombus is present. There is currently no evidence supporting the safety of doing so. However, there is also no definitive evidence demonstrating a link between antifibrinolytic use and thrombosis.[17,18] We therefore recommend that each case of hyperfibrinolysis be evaluated individually and the risks of potential thrombosis weighed against the benefits of treating hyperfibrinolysis with an antifibrinolytic. Here, we present the first published report of the successful treatment of hyperfibrinolysis with an antifibrinolytic in the setting of a recent ICT.

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