be avoided. Vasodilators such as nitroglycerin (and perhaps volatile anesthetics) may be contraindicated. Although a segmental intramural coronary artery can be managed with supraarterial myotomy or coronary bypass,[8-10] management of total intramural coronary arteries as in the current case has not been described.

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Fatal Pulmonary Embolism during Liver Transplantation

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FATAL pulmonary embolism is a very rare intraoperative complication of orthotopic liver transplantation (OLT), despite the use of antifibrinolytic agents in cirrhotic patients prone to hyperfibrinolysis in the setting of clotting activation and thrombin generation.[1] We report two such fatal complications to which aprotinin may have contributed.

Case Reports

Case 1

The patient was a 38-yr-old man with Laennec's cirrhosis and hepatitis C. Eight months before transplantation he presented with esophageal variceal bleeding and spontaneous bacterial peritonitis. He became progressively encephalopathic and short of breath and was admitted to the hospital. Laboratory studies included hematocrit,

21%; leukocyte count, $18.5 \times 10^3/mm^3$; platelet count, $103,000/mm^3$; and prothrombin time (PT) 16.3 s (INR, 1.6). The patient was hyponatremic, hyperkalemic, and oliguric, with creatinine level of 4.6 mg/dl, and required hemodialysis. Thoracentesis and paracentesis revealed negative bacterial cultures. He was treated with ciprofloxacin, and his leukocyte count fell to $9.4 \times 10^3/mm^3$.

The patient underwent an uncomplicated rapid sequence induction of anesthesia, after which a radial arterial catheter and two 9-French introducers were placed in the right internal jugular vein. Anesthesia was maintained with isoflurane and fentanyl, and dopamine was infused at $3 \mu g \cdot kg^{-1} \cdot min^{-1}$. The first hemodynamics recorded (before incision) were pulmonary artery (PA) pressure of 23/10 mmHg; CVP, 10 mmHg; and cardiac output (CO), 9.8 l/min. On FIO_2 of 0.6, first arterial blood gas (ABG) analysis revealed pH, 7.34; Pa_{CO2}, 35 mmHg; Pa_{O2}, 109 mmHg; base deficit, −5.7. Hct was 25%; PT, 19.1 s; and fibrinogen, 135 mg/dl. TEG is not used in our center. Before incision, 1 g/h infusion of ε-aminocaproic acid (EACA) was started after a 5-g bolus. Thirty minutes after incision, the patient experienced acute hypotension (systolic blood pressure, 65 mmHg) associated with rapid blood loss, which responded quickly to transfusion with 2 U packed red cells, 4 U fresh frozen plasma (FFP), 250 cc 5% albumin, and administration of $CaCl_2$ (500 mg) and phenylephrine (400 μg). After this episode, blood pressure was 130/75 mmHg, and PA was 41/23 mmHg; CVP, 14 mmHg; and CO, 12.7 l/min. The patient was hemodynamically stable through the rest of the dissection phase. Venovenous bypass with a heat exchanger and nonheparinized tubing was instituted without problems (flows, 2.1–2.5 l/min). Thirty minutes later, after hepatectomy, the surgeons noted extremely poor hemostasis and requested that aprotinin be given. The EACA infusion was discontinued, and after a test dose of aprotinin (10,000 KIU), the patient received a loading dose of 2 million KIU, followed by infusion of 200,000 KIU/h. Blood gas level a few minutes later (FIO_2 0.45) was pH, 7.4; Pa_{CO2}, 28 mmHg; Pa_{O2}, 218 mmHg, Hct, 25%; platelets, $37,000/mm^3$; PT, 16 s, and fibrinogen 154 mg/dl. Venous anastomoses were completed, and portal bypass was discontinued. Approximately 20 min after aprotinin was first given, the patient's blood pressure dropped acutely to 45/20 mmHg. Dopamine was increased to $10 \mu g \cdot kg^{-1} \cdot min^{-1}$, and boluses of epinephrine, neosynephrine, $CaCl_2$, sodium bicarbonate, and intravenous fluids were given with only transient improvement in blood pressure. PA pressures were also noted to be elevated to 50/29 mmHg, CVP to 29 mmHg, and CO could not be measured. End-tidal CO_2 dropped, and ABG on FIO_2 1.0 was pH, 7.49; Pa_{CO2}, 27 mmHg; Pa_{O2}, 47 mmHg, base deficit, −1.7. Venovenous bypass was discontinued, and the aprotinin infusion stopped. Large doses of pressors were administered without improvement.

A transesophageal echocardiographic (TEE) probe was placed and revealed a large right atrium and ventricle, with a large thrombus in the right atrium, through the tricuspid valve, and into the right ventricle. The right ventricle was severely hypocontractile, and the left ventricle appeared empty but normally contractile. Despite pharmacologic interventions, blood pressure continued to fall, and chest compression was begun, followed by direct myocardial compression for several minutes. One hour into the resuscitation, ABG on FIO_2 1.0 was pH, 7.12; Pa_{CO2}, 33 mmHg; Pa_{O2}, 75 mmHg; base deficit, −16.5. Systolic blood pressure never increased above 45 mmHg. The new liver was grafted and reperfused without any improvement in the patient's blood pressure. Cardiac surgeons were called and removed a large thrombus from the right

atrium and pulmonary artery, without bypass. Nonetheless, the patient died 2 h after the onset of hypotension.

Case 2

A 37-yr-old man with subacute hepatic failure of unknown cause presented 1 month before transplantation with fever, weakness, nausea, and vomiting. Hematocrit was 32%, platelets, $289,000/mm^3$; glucose, 57 mg/dl; creatinine, 1.4 mg/dl; albumin, 2.0 g/dl; and total bilirubin, 27.7 mg/dl. PT was 19.2 s; aspartate aminotransferase, 556 U/l; and alanine aminotransferase, 321 U/l—all significantly higher than 1 month previous. The patient's hospital course was significant for septic arthritis of the knee and bacteremia, managed with multiple antibiotics, and for spontaneous bacterial peritonitis. The patient's renal function deteriorated, and he was transferred to University of California, Los Angeles. He required hemodialysis, which was complicated by hypotension. Dopamine was administered for 8 days in dosages ranging from 3.5 to $7.5 \mu g \cdot kg^{-1} \cdot min^{-1}$. Dobutamine stress echo showed an ejection fraction of 55–60%.

The patient underwent an uncomplicated liver transplantation, during which 10 U packed cells, 17 U FFP, 20 U platelets, and 10 U of cryoprecipitate were given. He received aprotinin (2 million KIU bolus, 500,000 KIU/h) from the dissection phase through the end of surgery. The postoperative course was complicated by renal failure requiring dialysis and poor graft function. Two days later, the patient underwent a second liver transplantation for primary nonfunction.

After induction of anesthesia, aprotinin was administered in the same dose as for the first transplantation. Dissection and institution of venovenous bypass were uncomplicated. After hepatectomy, the patient developed acute systemic hypotension, and PA pressures rose suddenly to 40/30 mmHg. The surgeons noted a poorly contracting right ventricle (compared with normal hyperdynamic contractions), and PA pressures remained increased. The hypotension was unresponsive to dopamine, $8 \mu g \cdot kg^{-1} \cdot min^{-1}$, atropine given when the heart rate fell to 45 beats/min, and boluses of epinephrine. For these reasons, TEE was placed. A large thrombus was seen in the inferior vena cava and right atrium. Cardiac surgery consultants elected to remove the thrombus, and the patient was placed on cardiopulmonary bypass with heparin anticoagulation. Cardiotomy was performed, and large clots (some appearing fibrinous and likely to be days old, some appearing newly formed or gelatinous) were removed from the inferior vena cava, right atrium and ventricle, and pulmonary artery. After cardiopulmonary bypass, the patient required large doses of epinephrine, and then norepinephrine, to maintain blood pressure. The liver graft was placed without improvement in the pressor requirement. Hemostasis in the neohepatic phase was poor despite administration of cryoprecipitate, FFP, and 100 mg of protamine. New thrombus was noted on TEE in the RA and RV and attached to the PA catheter, and so, further protamine and antifibrinolytics were not given (despite partial thromboplastin time [PTT] > 180 s). Cardiac surgeons did not believe a second procedure was indicated. The patient received 36 U each of packed cells and FFP. The patient was transported to the intensive care unit on a norepinephrine infusion ($2 \mu g \cdot kg^{-1} \cdot min^{-1}$). He never regained consciousness and was declared brain dead on the second postoperative day.

Discussion

The two cases presented here occurred within 1 month of each other, at a time just after the introduction

CASE REPORTS

of aprotinin into clinical use during OLT; 15 patients before these received aprotinin during OLT. Before this time, the standard antifibrinolytic regimen during OLT at our center was EACA, given to more than 600 patients without evidence of abnormal clot formation. The proximity of these cases in our center is striking and should motivate reevaluation of antifibrinolytic therapy during liver transplantation.

Liver transplantation centers vary in their practice of administration of procoagulant drugs. EACA is probably the most commonly administered antifibrinolytic drug in the United States for patients undergoing OLT. A combination of release of tissue plasminogen activator (t-PA) from graft endothelium and decreased hepatic clearance of t-PA generally is accepted as one contributor to enhanced fibrinolysis during liver transplantation.[2] Thus, EACA is used during liver transplantation for its effect of interfering with plasmin(ogen) binding to fibrin. Almost a decade ago, the drug was reported to reverse thromboelastographic evidence of fibrinolysis without causing thrombotic complications during liver transplantation.[3] Although EACA was not rigorously, prospectively studied, such reports influenced clinical practice tremendously. A prospective study on EACA was reported at a national meeting[4] and greatly influenced our local practice. In this blinded study, transfusion requirements were significantly decreased when EACA was given to patients undergoing liver transplantation (5-g bolus, then 1- g/h infusion). This study caused our center to standardize the administration and dose of EACA.

Several reports from outside the United States suggested that the antifibrinolytic drug, aprotinin, was effective in reducing transfusion requirements during OLT. A 50% reduction in transfusion requirements was reported when aprotinin (2 million KIU bolus, then 500,000 KIU/h infusion) was given during liver transplantation.[5] However, this study was small and used retrospective control subjects. Similar problems plague other reports,[6-9] and further, drug dose is not standardized from report to report.[10,11] Recent studies have helped elucidate some of the mechanisms of aprotinin action during liver transplantation, such as its antikallikrein effect,[12] but the number of patients prospectively studied against either placebo or EACA has not been large. Nonetheless, aprotinin is used routinely in many European liver transplantation centers, and some authors report that they will not study the drug with a control arm because withholding aprotinin would be

unethical.[13] Not all studies support a role for aprotinin in reducing transfusion requirements during OLT.[14]

One case report increased concern that aprotinin contributed to a fatal pulmonary embolism during OLT.[15] This patient (after receiving a bolus of aprotinin 1.6 million KIU and an infusion at 0.5 million KIU/h) developed a large thrombus attached to the pulmonary artery catheter, spanning the superior vena cava into the pulmonary artery. The authors suggested that the complication may have been a result of very low antithrombin III levels and of two introducers in the internal jugular vein leading to endothelial activation. Further, in a report of six perioperative liver transplantation deaths attributed to pulmonary platelet aggregates, three of the six patients received aprotinin, and two of these died during surgery.[16]

Rare cases of pulmonary embolism during OLT have been reported before the use of aprotinin.[17-19] Another report increased concern that EACA may contribute to rare pulmonary embolism.[20] Two of 12 patients who had received EACA experienced massive thromboembolism during transplantation. Of note, both patients were critically ill and intubated before surgery.

In the two cases reported here, several factors may have contributed to abnormal clot formation. The first patient received EACA followed by aprotinin, and it is possible that the drugs had a synergistic action on clot formation. The second patient was septic in the weeks before transplantation. If he had ongoing infection, disseminated intravascular coagulation (DIC) may have contributed to clot formation. In addition, patients with acute liver disease may be more prone to DIC than those with chronic disease.[21] Drug dosage may be a factor. A recent prospective study of aprotinin suggests that much lower dosages (0.2 million KIU/h infusion without a bolus) than originally reported may be sufficient to decrease fibrinolytic activity during liver transplantation,[22] increasing concern that high- dose aprotinin may be an unnecessary risk. The timing of the second transplantation may have placed the second patient at risk for clotting complications because there may be a relative abundance of procoagulants (such as plasminogen activator inhibitor) and slow recovery of protein C and S several days after OLT.[23]

In summary, the complicated coagulopathy in liver disease combined with an equally complex superimposed coagulopathy during surgery are inherently difficult to study. For example, there often is insufficient clinical information to clearly distinguish between primary and secondary fibrinolysis in these patients. Large

432

CASE REPORTS

prospective trials to determine optimal antifibrinolytic therapy are needed to determine minimal effective doses and to carefully document the balance between thrombogenic factors and antifibrinolytic parameters after drug administration. In experienced transplantation centers, aggressive transfusion therapy of coagulopathy combined with potent procoagulant drugs may lead to increased thrombotic complications. These cases highlight the need for a reevaluation of procoagulant therapy during liver transplantation.

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