

Anaphylaxis Complicating Graft Reperfusion During Orthotopic Liver Transplantation: A Case Report

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ABSTRACT

Hemodynamic instability may occur during liver transplantation especially following unclamping the portal vein. A period of hypotension (postreperfusion syndrome) is usually responsive to treatment with fluids, calcium, sodium bicarbonate, and vasoactive drugs, but if hypotension persists, other causes must be sought out. In this report, we present a case in which anaphylaxis, most likely due to a component of the University of Wisconsin preservation solution, occurred coincident with liver reperfusion and severely exacerbated reperfusion hemodynamic instability. To our knowledge, this is the first report of anaphylaxis at the time of reperfusion and may provide an explanation for cases of vasoplegic syndrome associated with graft reperfusion.

HEMODYNAMIC INSTABILITY may occur during liver transplantation when the portal vein is unclamped and blood flow is established through the donor liver. Severe hypotension that may follow can be part of the postreperfusion syndrome (PRS) or simply, reperfusion hypotension. PRS is defined as a decrease in mean arterial pressure of >30% for more than 1 minute within the first 5 minutes following portal vein unclamping.^{1,2} PRS is usually responsive to treatment with fluids, calcium, sodium bicarbonate, and vasoactive drugs such as epinephrine and norepinephrine.³ If hypotension persists, other causes such as myocardial dysfunction, pulmonary thromboembolism, air embolism, hemorrhage, or primary graft nonfunction must be ruled out. In this report, we present a case in which anaphylaxis, most likely to a component of the University of Wisconsin (UW) preservation solution, occurred coincident with liver reperfusion and severely exacerbated reperfusion hemodynamic instability. To our knowledge, this is the first report of anaphylaxis at the time of reperfusion and may provide an explanation for cases of vasoplegic syndrome associated with graft reperfusion.

CASE REPORT

A 45-year-old man with end-stage liver disease (ESLD) secondary to chronic hepatitis C infection and ethanol abuse presented for orthotopic liver transplantation with a Model for End-Stage Liver Disease score of 38. Refractory ascites, encephalopathy, and upper gastrointestinal bleeding, treated with esophageal variceal banding, had complicated his ESLD. He had no history of drug allergy. Preoperative cardiac workup, including transthoracic echocardiography and nuclear perfusion scan, showed hyperdynamic left ventricular

function and no evidence for increased pulmonary artery pressures or myocardial perfusion defects.

After premedication with midazolam, the patient was taken to the operating room, standard monitors were placed, and anesthesia was induced with propofol, rocuronium, and fentanyl. The trachea was intubated and the patient was mechanically ventilated using volume control ventilation (tidal volume 450 mL, rate 12 breaths/min, positive end-expiratory pressure [PEEP] 5 cm H₂O, F_iO₂ 1.0, peak inspiratory pressure 25 cm H₂O). General anesthesia was maintained with desflurane in oxygen and a fentanyl infusion. After induction, the patient required two doses of phenylephrine (100 µg each) to maintain an adequate blood pressure. Additional vascular access for transfusion and invasive monitoring was obtained with an arterial line in the left radial artery, and two central venous lines placed in the right internal jugular vein. Cefotaxime (2 g) was given prior to incision, and a loading dose of solumedrol (1 g) was given per transplant protocol.

The surgeon team proceeded with the dissection phase of the operation with the intention of grafting the donor liver using piggyback technique. Peak airway pressures decreased after evacuation of 13.5 L of ascites. Platelets, fresh frozen plasma, and washed red blood cells were administered as indicated by laboratory values; 1000 mL of 5% albumin was also given to maintain preload. Low-dose phenylephrine (35 µg/min) and dopamine (2.5 µg/kg/min) infusions kept the systolic blood pressure in the 90 to

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100 mm Hg range. Entrance into the anhepatic phase was associated with minimal hemodynamic changes, as expected for the piggyback approach, which avoids complete clamping of the inferior vena cava. Prior to grafting, the donor liver was flushed with 1000 mL of 6% hetastarch. The hepatic veins and portal vein were anastomosed to the recipient vena cava and portal vein, respectively. Throughout the anhepatic phase, the blood pressure was stable without the need to increase the vasoconstrictor infusion rate. Upon unclamping the portal vein, blood pressure rapidly decreased to 70/40 mm Hg over a 1- to 2-minute period, associated with a heart rate decrease from 70 to 60 beats per minute. This anticipated episode of hypotension was treated with bolus injections of epinephrine (20 μ g) and NaHCO_3 (50 mEq) and infusion of washed red blood cells (500 mL). Blood pressure recovered quickly, returning to a systolic pressure of 90 to 100 mm Hg and remained stable for the next 3 minutes. Systolic blood pressure then rapidly declined again to 60 to 70 mm Hg, associated with a heart rate increase to more than 100 beats per minute. Increased peak airway pressures (40 cm H_2O) were noted, and physical examination revealed marked swelling of the patient's face, lips, and tongue as well as coarse breath sounds bilaterally. Additional bolus injections of epinephrine (1266 μ g total) were administered, and infusions of norepinephrine (8 μ g/min) and epinephrine (4 μ g/min) were initiated. The phenylephrine infusion had also been increased to 150 μ g/min. Transesophageal echocardiography exam revealed adequate filling volumes, excellent left ventricular function, normal right ventricular and atrial size and function, and no acute valve pathology. High peak airway pressures persisted and six puffs (~500 μ g) of albuterol were administered via the endotracheal tube and PEEP was increased to 10 cm H_2O . Despite administration of more volume and high-dose phenylephrine, norepinephrine, and epinephrine infusions, hypotension persisted. After 15 minutes of resuscitative efforts, pulse oximeter saturations began to decrease. With the patient receiving an $\text{F}_i\text{O}_2 = 1.0$, an arterial blood gas showed metabolic and respiratory acidosis and hypoxemia with a pH of 7.10, pCO_2 50 mm Hg, pO_2 78 mm Hg, bicarbonate 15.5 mEq/L, base deficit -13.6, and arterial saturation of 89%. Administration of vasopressin (40 U) as intravenous bolus, resulted in immediate improvement of blood pressure and oxygen saturation. A vasopressin infusion was then started and maintained at 0.08 U/min. Further diagnostic information was obtained from a pulmonary artery catheter passed through an internal jugular vein introducer, revealing pulmonary artery pressures of 40/15 mm Hg with a mean of 26 mm Hg and a wedge pressure of 15 mm Hg. Cardiac output measured by thermodilution was 13 L/min, giving a calculated systemic vascular resistance of 338 dyne $\cdot$ s/cm⁵. Both parameters were consistent with the hyperdynamic state displayed by the TEE exam.

While surgery continued with arterial and biliary anastomoses, the vasopressor dependence remained constant. The face, lips, and tongue of the patient showed persistent swelling and rubor. A serum sample was sent to the clinical laboratory to quantify the tryptase level and a previously sent tropinin I level returned at 0.11 μ g/L (normal range < 0.05 μ g/L). Cimetidine and diphenhydramine were then administered based on our suspicion for anaphylaxis. The peak airway pressures slowly returned to normal, and oxygenation normalized on serial arterial blood gas analyses. Metabolic acidosis slowly improved with administration of additional volume and sodium bicarbonate.

By the end of the operation, the liver graft was excreting bile and vasopressor requirement to maintain adequate blood pressure had decreased. The patient was transported to the intensive care unit

on epinephrine (2 μ g/min), norepinephrine (2 μ g/min), and dopamine (1 μ g/kg/min). Over the next 12 hours, the vasopressors were further weaned with the norepinephrine being the last to be discontinued. Facial and upper airway swelling resolved, and the patient's trachea was extubated the next day. He showed rapid improvement in urine output, renal function, and neograft function postoperatively, and he was discharged to home on postoperative day 8.

The tryptase level reported 14 days later showed a total tryptase of 34 ng/mL (normal range 1–15 ng/mL) and a beta-tryptase level of 19 ng/mL (normal range $\leq$ 1 ng/mL). These values were determined by the accepted test using monoclonal antibodies specific for alpha and beta tryptase in an enzyme-linked immunosorbent assay.⁴

DISCUSSION

In this case severe, refractory hypotension occurred at the time of neograft reperfusion during orthotopic liver transplantation. The constellation of facial rubor and edema, bronchospasm, peripheral vasodilation, and positive mature (beta) tryptase levels strongly indicated that an anaphylactic reaction was triggered at the time of portal vein unclamping, most likely due to one of the components of the UW preservation solution or to hetastarch used to flush the donor liver.

Although some of these physical signs occur regularly as part of a typical PRS, the time course of the reaction raised our suspicion of an additional pathological reaction. In our experience, PRS usually responds to infusion of fluids, positioning (head down), and vasopressor administration. Once initial hypotension begins to reverse, the prognosis for hemodynamic stability is favorable. In this case, a secondary drop in pressure along with bronchospasm, facial angioedema, worsening acidosis and hypoxemia immediately followed initial improvement in blood pressure with these standard treatments. At that point, the differential diagnosis expanded to include myocardial dysfunction, occult bleeding, electrolyte abnormality, pulmonary embolism (air, thrombus, fat), anaphylaxis, sepsis, or primary non-function of the donor liver.

All of these causes were ruled out at the time except for anaphylaxis. Transesophageal echocardiography and pulmonary arterial catheterization revealed adequate myocardial function, with normal chamber sizes and pressures in the setting of a high cardiac output. In particular, the absence of right ventricular strain eliminated pulmonary embolization as a cause. Bronchospasm resolved after administration of β_2 agonist (albuterol). Serum electrolyte values were within the normal range. There was no evidence of massive bleeding in the surgical field. Over the course of hours, the circulation improved after treatment with H-1 and H-2 blockers, and the patient could be successfully weaned off pressors and showed no ongoing signs of sepsis. By the end of the procedure, the liver graft had begun clearing acid load, and there were no signs of acute rejection postoperatively. The most likely diagnosis that unified the physical findings remained anaphylaxis. This diagnosis is further supported by the measurement of

an elevated serum beta tryptase level, drawn after reperfusion, indicating systemic mast cell degranulation.⁵

Elevated mature tryptase level is a highly specific finding in anaphylaxis⁶ and identifies the cause of prolonged cardiovascular instability at the time of reperfusion in our case compared to other cases of vasoplegic syndrome during liver transplantation.^{7,8} Tryptase, a protease, is the predominant component in the secretory granules of mast cells. The total tryptase level (alpha plus beta) was elevated at 34 ng/mL. Elevated alpha tryptase can be a marker for increased total number of mast cells, as found in systemic mastocytosis, but an elevated beta tryptase is specific for mast cell degranulation, as occurs in anaphylaxis. Mast cell degranulation during liver transplantation due to other causes, such as ischemia or adenosine-mediated release, has not been reported. In fact, a study by Woehlck et al found no significant elevation of beta tryptase in patients undergoing routine orthotopic liver transplantation.⁹ They hypothesized that small increases in beta tryptase might not be detectable because of hemodilution and insufficient hepatic mast cell numbers. Therefore, the elevated level of beta tryptase we found indicated that massive, systemic mast cell degranulation occurred in this patient.

The exact trigger for anaphylaxis in this case remains unknown. Because the reaction occurred right after release of the portal vein clamp, an ingredient of the UW preservation solution or hetastarch flush is the most likely culprit. The elements of UW solution are shown in Table 1. Three of the components listed—allopurinol, adenosine, and hydroxyethyl starch—have been previously reported as anaphylaxis triggers.^{10–13} Adenosine may be able to cause direct mast cell degranulation, but Woehlck et al could not

demonstrate that this mechanism produced significant elevation of beta tryptase in their case series.⁹ We also cannot rule out a reaction to washed red blood cells that were given at the time of portal vein unclamping. However, portions of the same washed red blood cell units had been given earlier in the procedure by our rapid infusion device without a reaction. In addition, two earlier studies of transfusion allergy cases failed to demonstrate significant tryptase elevation in association with these types of reaction.^{14,15} If this particular patient would need to be retransplanted in the future, use of an alternative organ preservative such as histidine-tryptophan-ketoglutarate solution should be strongly considered. The case also illustrates the need to search diligently for all possible causes for persistent PRS.

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Table 1. Allergic Potential of Components of University of Wisconsin Solution

Component	Evidence for Cause of Anaphylaxis	Reference
Potassium lactobionate (100 mmol/L)	None: bis-lactobionyl conjugate unable to elicit anaphylactic reactions	10
Potassium phosphate (25 mmol)	—	—
Magnesium sulfate (5 mmol/L)	—	—
Raffinose (30 mmol/L)	None	—
Adenosine (5 mmol/L)	Case report with (+) tryptase	11
Glutathione (3 mmol/L)	None	—
Allopurinol (1 mmol/L)	Anaphylactic cross-reaction to enalapril	12
Hydroxyethyl starch (50 g/L)	Anaphylaxis temporally related to administration but (–) skin testing	13