

Anaphylaxis on Reperfusion During Liver Transplantation with Coagulopathy

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We present a case in which anaphylaxis on hepatic reperfusion during liver transplantation presented only with hypotension and coagulopathy. There were no cutaneous manifestations or clinical features distinguishing anaphylaxis from postreperfusion syndrome. The recipient regularly consumed seafood, and the organ donor died of anaphylaxis to shellfish. The trigger for anaphylaxis was postulated to be passive transfer of immunoglobulin to the recipient. Anesthesiologists should be notified of donor factors to anticipate anaphylaxis. In this report, we discuss coagulopathy of anaphylaxis and contrast it with disseminated intravascular coagulation. (*Anesth Analg* 2012;115:522–5)

There are 2 reports of anaphylaxis on neohepatic reperfusion during liver transplantation (LTx),^{1,2} with manifestations including bronchospasm, vasoplegia, and angioedema. Anaphylaxis and severe postreperfusion syndrome share many features, such as vasoplegic hypotension and coagulopathy. Typical laboratory abnormalities of coagulopathy of postreperfusion syndrome, disseminated intravascular coagulation (DIC), and coagulopathy after anaphylaxis overlap.

CASE REPORT

A 62-year-old, 185-cm, 92-kg Caucasian man with hemochromatosis, hepatocellular carcinoma, and cirrhosis, presented for LTx. Pulmonary function testing revealed mild restriction without obstruction. The patient denied drug, food, or environmental allergies. Sequential therapeutic phlebotomy to the point of microcytic anemia reduced his ferritin to <50 µg/L at the time of transplantation. His baseline laboratory values were unremarkable, except for a platelet count of 78,000.

The 24-year-old organ donor suffered anoxic brain death from anaphylaxis after ingestion of shellfish; laryngeal edema delayed initial intubation and resuscitation. All signs of anaphylaxis had resolved approximately 10 days before organ donation.

The recipient underwent orthotopic LTx using venovenous bypass (VVB). His baseline mean arterial blood pressure (MAP) was 73 mm Hg, heart rate 105, cardiac output 4.6 L/min, and systemic vascular resistance 1100 dynes · s · cm⁻⁵. Before initiating VVB, the fibrinogen was 162 mg/dL, and the international normalized ratio was 1.2.

The dissection and anhepatic stages were uneventful, and 500 mg methylprednisolone was administered on VVB. After hepatic reperfusion, initial bradycardia responded to 50 µg epinephrine, and the MAP was maintained at 70 to 80 mm Hg with phenylephrine for a few minutes. Despite the absence of clinical bleeding and several additional milligrams of phenylephrine, the MAP decreased to 34 mm Hg, cardiac output >15 L/min, and systemic vascular resistance <150 dynes · s · cm⁻⁵. Ten units of vasopressin had minimal effect. Methylene blue (1 mg/kg) was ineffective. No wheezes were audible, although capnography revealed mild obstruction with peak airway pressures that increased from 27 to 33 cm H₂O. His blood pressure responded to 25 mg IV diphenhydramine and an additional 150-µg bolus of epinephrine, and was maintained with an additional 2 mg/kg methylene blue and an infusion of epinephrine at 0.05 µg/kg/min for the remainder of the LTx. Several minutes postreperfusion, a severe coagulopathy with clinical bleeding developed; thrombelastography was started 20 minutes after reperfusion. No clot occurred with kaolin activation, and minimal delayed clot formed with rapid fibrinolysis in the kaolin-activated sample with heparinase, indicating the presence of heparin. The coagulation laboratory reported critical values or potential error with no clot formation. The fibrinogen was <60 mg/dL, international normalized ratio >10, D-dimers were 11.5 mg/L, and platelet count was 43,000. Treatment included 500 mg ε-aminocaproic acid for fibrinolysis, 50 mg protamine to counteract heparin; coagulation factors were replaced with cryoprecipitate, fresh frozen plasma, platelet rich plasma, and packed red blood cells. Serum tryptase was drawn 45 minutes after reperfusion. Urticaria was absent, but severe bowel edema without liver congestion delayed abdominal closure. Coagulation improved within 3 hours as determined by laboratory values, repeat thrombelastography, and reduced clinical bleeding. The patient recovered and was discharged to home; his health care power of attorney gave written consent for publication of the case report, and also revealed that the patient routinely ate seafood.

The serum total tryptase was 493 ng/dL (normal 0.0–11.49) confirming intraoperative anaphylaxis; 2 weeks later, a total tryptase was 6.5 ng/dL, excluding systemic mastocytosis in the recipient. Intraoperative hepatic biopsies obtained after reperfusion and 16 hours later were

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stained with and were negative for CD117 for mast cells, and CD61 (anti-integrin β -3) for platelet thrombi. These biopsies excluded systemic mastocytosis in the donor and microvascular thrombosis in the recipient.

DISCUSSION

Three distinct clinical entities warrant comment: the triggering of anaphylaxis, the occult presentation of anaphylaxis and its overlap with postreperfusion syndrome, and coagulopathy. Transfusion of blood products from food-allergic donors may cause transient allergy through transfer of immunoglobulin (Ig)E, even if the allergen was consumed by the recipient days before antibody transfer.³ Liver and lung transplantation from donors dying of anaphylaxis or with severe allergies are associated with delayed³ transfer of allergy,^{4,5} which may result from IgE producing plasma cells that survive in these organs after transplantation.³ The contribution of preformed IgE remains uncertain,³ but serum IgE will increase within 2 weeks of mucosal antigen challenge.⁶ Although donor IgE was unmeasured, the timing of organ procurement was consistent with an antigen-stimulated increase in donor IgE,⁶ potentially increasing the risk for immediate allergic reactions through transfer of preformed IgE.³ Therefore, caution is required when donors have anaphylactic reactions, because this clinical setting may indicate higher risk for anaphylactic reactions on reperfusion through the transfer of IgE.

Unless future research identifies that severe postreperfusion syndrome actually is a manifestation of anaphylaxis or a nonimmunologic release of mast cell mediators,⁷ the presentation of anaphylaxis in this patient was occult, because bronchospasm most consistently distinguishes anaphylaxis from postreperfusion syndrome.^{1,2} In this case and more than half of anaphylactic events during anesthesia,⁸ bronchospasm was minimal. Although confirmed by tryptase, the paucity of clinical signs prevented this case from satisfying diagnostic clinical criteria of anaphylaxis.⁹ Only in retrospect did the acute improvement in hemodynamics after treatment with epinephrine and diphenhydramine further support a diagnosis of anaphylaxis. Bowel edema was consistent with gastrointestinal mast cell activation and a food-borne antigen.³ Hypotension and coagulopathy are common to both syndromes, rendering tryptase the only means of confirming anaphylactic events. At our institution, 2 confirmed cases of anaphylaxis during LTx were associated with severe, acute reperfusion coagulopathy.¹ The absence of reperfusion coagulopathy or severe postreperfusion syndrome ($n = 6$) was associated with normal tryptase levels.¹⁰

β -Tryptase, histamine, and heparin are the major components of mast cell granules¹¹; prostaglandin D₂, leukotrienes, platelet-activating factor (PAF), other cytokines, and proteases are typically minor components or are produced only by some mast cell subtypes.^{10–12} Heparin and tryptase effects account for the coagulopathic features of this patient. Some heparin is typically released from liver grafts at reperfusion, being residual from heparin given during organ procurement. However, mast cells were not seen in this donor liver and are rare in noncirrhotic human liver parenchyma,¹³ and therefore the donor liver could not

contain sufficient endogenous heparin to fully anticoagulate the recipient. Other tissues, including skin and the respiratory and digestive tracts,¹³ contain vastly more mast cells; systemic heparinization is consistent with heparin release from the recipient, not donor mast cells.

Tryptase contributes to coagulopathy by degrading fibrinogen,¹¹ and activating urokinase that activates plasminogen, causing fibrinolysis.¹⁴ Tryptase also initiates fibrinolysis by degrading high-molecular-weight kininogen to bradykinin, which stimulates the vascular B2 kinin receptor,¹⁵ releasing endothelial stores of tissue plasminogen activator (t-PA) and von Willebrand factor (vWF)¹⁶ into the circulation. Plasmin generated by t-PA also cleaves high-molecular-weight kininogen to bradykinin, amplifying the response.¹⁷ Bradykinin vasodilates via the endothelial release of nitric oxide and prostacyclin. Angiotensin-converting enzyme inhibition augments these effects by increasing bradykinin concentrations.^{15,17} There are opposing platelet effects, as high vWF levels increase platelet adhesion, but prostacyclin reduces platelet function. Prostacyclin and t-PA have short half-lives, but vWF persists beyond 24 hours and may contribute to thrombotic complications of LTx after resolution of the initial coagulopathy.^{18,19} Anaphylaxis-initiated thrombosis and vasospasm occur more frequently in Kounis syndrome (allergic angina).²⁰

Insect sting anaphylaxis also causes coagulopathy²¹; similar coagulopathies occur during tumor lysis of basophilic leukemia.²² Although mature mast cells contain tryptase, basophils contain histamine and heparin but minimal tryptase. Therefore, tumor lysis of basophilic leukemia causes anticoagulation but not fibrinolysis or hypofibrinogenemia. Inconsistent terminology across specialties impedes recognition of coagulopathy due to anaphylaxis; Roizen et al.²³ reported DIC and anaphylaxis to a vascular graft. Laboratory evidence of DIC and coagulopathy after anaphylaxis overlap, although the mechanisms differ. Fibrin degradation products may be low in nonsurgical patients with coagulopathy after anaphylaxis,²¹ but could be higher in surgical patients when vascular grafts provide focal (not disseminated) intravascular sites of platelet adhesion and clot formation. In our patient, biopsy excluded microvascular thrombosis, making the evidence consistent with coagulopathy after anaphylaxis, not DIC. Histamine concentrations correlate with tryptase levels,⁷ and a small amount of literature suggests that the severity of an anaphylactic reaction may also correlate with tryptase,^{2,21,24,25} or PAF levels.^{26,27} Preliminary reports suggest that montelukast and antihistamines, particularly antihistamines blocking PAF (rupatadine) reduce anaphylactic severity and mediator release.^{28–31}

There already are potential therapeutic inhibitors of coagulopathy after anaphylaxis, and they have a role in the treatment of reperfusion coagulopathy in current practice. Heparin and tryptase are the 2 agents currently documented to initiate coagulopathy. Neutralization of heparin by protamine is already standard treatment.³² Because tryptase requires the presence of heparin to retain activity,¹¹ protamine also terminates tryptase-mediated effects.³³ There may be reluctance to administer protamine because it can initiate anaphylactic reactions, but when

used as treatment for anaphylaxis, the initiation of anaphylaxis becomes a moot point. Aprotinin inhibits tryptase, improving coagulation during LTx.³⁴ Nafamostat, a nonpeptide broad-spectrum protease inhibitor, reduces hemodynamic instability during LTx³⁵ and improves coagulopathy of DIC,³⁶ but is used at doses far higher than needed for specific tryptase inhibition,³⁷ which may account for its anticoagulant effects.

In summary, anesthesiologists should be notified if the organ donor experienced an anaphylactic reaction, because LTx recipients may be at higher risk of anaphylaxis through transfer of IgE. Anesthesiologists should be aware that features of postreperfusion syndrome and anaphylaxis overlap, because therapy or prophylaxis for anaphylaxis may be beneficial. Finally, the coagulopathy of anaphylaxis can be confused with DIC, but is an entity requiring specific treatment. ■■

DISCLOSURES

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Contribution: This author helped analyze the data, write the manuscript, and provided direct patient care.

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