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## CLINICAL INFORMATION

# Fulminant hepatic failure after simultaneous kidney-pancreas transplantation: a case report



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### PALAVRAS-CHAVE

Insuficiência  
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**Abstract** We describe an unusual case of hyperacute hepatic failure following general anesthesia in a patient receiving a simultaneous kidney-pancreas transplant. Despite an aggressive evaluation of structural, immunological, viral, and toxicological causes, a definitive cause could not be elucidated. The patient required a liver transplant and suffered a protracted hospital course. We discuss the potential causes of fulminant hepatic failure and the perioperative anesthesia management of her subsequent liver transplantation.

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### Insuficiência hepática fulminante após transplante simultâneo de rim-pâncreas: um relato de caso

**Resumo** Descrevemos um caso incomum de insuficiência hepática hiperaguda após a anestesia geral em uma paciente que recebeu um transplante simultâneo de rim-pâncreas. Apesar de uma avaliação agressiva das causas estruturais, imunológicas, virais e toxicológicas, uma causa definitiva não pôde ser identificada. A paciente precisou de um transplante de fígado

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que resultou em prolongamento da internação hospitalar. Discutimos as potenciais causas da insuficiência hepática fulminante e o manejo da anestesia no período perioperatório de seu subsequente transplante de fígado.

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## Introduction

Hepatotoxicity has long been recognized as an adverse effect of halogenated volatile anesthetic metabolism. The development of newer agents that undergo less hepatic metabolism has greatly decreased its incidence in modern anesthesia. Classically described as the onset of postoperative fever, myalgias, rash, and jaundice 48–72 h following exposure, volatile hepatotoxicity is associated with significant morbidity and mortality. To the best of our knowledge, we describe the first case of hyperacute liver failure following isoflurane exposure. Our patient developed overt liver failure within 24 h of exposure, and required a liver transplant on postoperative day 2. We describe our workup and review volatile hepatotoxicity. All patient information has been adequately deidentified in accordance with Mayo Clinic IRB and institutional policy, as well as, the Health Insurance Portability and Accountability Act.

## Case report

A 60-year-old Asian female with end stage kidney disease secondary to diabetes and hypertension presented for a simultaneous kidney-pancreas transplant. Her past medical history was notable for chronic anemia, latent TB (treated with isoniazid 2 years prior), hepatitis B core antibody positive without a detectable viral load, mild pulmonary hypertension, ocular stroke, and coronary artery disease status-post drug eluting stent placement. She had a left upper arm arterio-venous fistula at an outside facility, presumably with a general anesthetic, however her medical records were not available for review. Her kidney-pancreas transplant proceeded uneventfully after induction with propofol (120 mg), fentanyl (250 mcg), and midazolam (2 mg) followed by isoflurane, hydromorphone (1 mg), and cis-atracurium (36 mg over 436 min) for maintenance of anesthesia. Expiratory isoflurane concentration was maintained between 1.0% and 1.5% throughout the case. The intraoperative anti-rejection regiment consisted of a thymoglobulin infusion and 500 mg of methylprednisolone. The patient began producing urine and the blood glucose decreased following reperfusion of the kidney and pancreas respectively. There were no prolonged hypotensive episodes. One unit of packed red blood cells was transfused

intraoperatively for a hemoglobin of 7.3 g.dL<sup>-1</sup>. The total anesthetic time was 436 min and the surgical time was 339 min. The post-anesthesia care unit course was uneventful and the patient was transferred to the floor.

The following morning, the patient was found to be very lethargic, but arousable. Laboratory results revealed elevated liver function tests (LFTs) with aspartate aminotransferase (AST) 3904 IU.L<sup>-1</sup> and alanine aminotransferase (ALT) 2596 IU.L<sup>-1</sup>, up from 23 IU.L<sup>-1</sup> and 31 IU.L<sup>-1</sup> preoperatively. She was transferred to Intensive Care Unit (ICU) with a diagnosis of acute liver failure and intubated secondary to rapidly worsening encephalopathy. Urine output progressively decreased and continuous renal replacement therapy was initiated. Additionally, a metabolic acidosis developed, requiring treatment with a bicarbonate infusion. On Post-Operative Day (POD) 2, LFTs peaked, at AST 58,960 and ALT 6684, and the International Normalization Ratio (INR) also increased to 5.8 (baseline 1.0). The patient was listed as Status 1 for liver transplantation, indicating severe liver disease with a life expectancy of hours to days. Concurrently, the patient received an aggressive work-up to determine the cause of liver failure. Immunological, viral, structural, and toxicology studies were all nondiagnostic. An intense review of the patient's medications was performed to identify medication with hepatotoxic potential. On POD 2, the patient underwent a liver transplant. With the possibility of isoflurane being the cause of the patient's idiosyncratic reaction, the anesthesia team decided to forego inhalational anesthesia and opted for a total intravenous anesthesia approach. Infusions of propofol (50–100 mcg.kg<sup>-1</sup>.min<sup>-1</sup>) and midazolam (0.25–0.5 mg.h<sup>-1</sup>) were employed, with titration to maintain the bispectral index monitor between 10 and 40. Additionally, cis-atracurium and fentanyl boluses were administered as needed. Continuous renal replacement therapy was maintained in the operating room. The orthotopic liver transplantation was performed using a piggy-back technique and was uneventful with the exception of a mild reperfusion syndrome following recirculation that required the brief addition of a vasopressin drip.

On visual inspection, the liver appeared grossly necrotic. Pathological examination of the explant revealed submassive necrosis, characterized by large areas of confluent multilobular necrosis, as well as, centrilobular and bridging necrosis and a background of hepatocellular hemosiderosis. Viral inclusions were not seen.

The patient had a rather complicated recovery, although liver graft function was preserved. Postoperative complications included several return trips to the operating room for increased intra-abdominal pressures, hematoma evacuation, and abdominal washout. She suffered a cardiac arrest secondary to hypoxic respiratory failure on POD 10. Renal function improved and dialysis was discontinued on POD 24. She was briefly discharged from the hospital on POD 34. However, she soon returned and began a protracted hospital course with neutropenic fever, and an intraabdominal abscess ultimately resulting in allograft pancreatectomy. She has steadily improved following her pancreatectomy and is currently doing well.

## Discussion

Fulminant hepatic failure is defined as rapidly progressing liver failure with hepatocellular necrosis, an increase in the INR greater than 1.5, and any level of encephalopathy in a patient without prior liver disease.<sup>1</sup> Acute hepatic failure following general anesthesia is a rare event in patients without pre-existing liver disease and typically carries a high mortality rate. While an idiosyncratic drug reaction was our working diagnosis, the case was clinically perplexing in the rapidity of onset and degree of liver failure without an obvious inciting event. The list of potential causes is extensive; however, we will focus on more common causes in our discussion.

Our patient's hepatic deterioration was rapid, occurring within 24 h of the original kidney-pancreas transplant surgery, leaving a small window for potential structural causes. There was no vascular injury during the surgery and intraoperative blood loss was not significant enough to be a likely cause of hepatic blood flow compromise. The intraoperative hemoglobin was maintained between 7.3 and 9 g.dL<sup>-1</sup>, from a preoperative baseline of 11.2 g.dL<sup>-1</sup>. When postoperative hepatic dysfunction was identified, repeat radiographic evaluation with ultrasound and computed tomography showed no new gross abnormalities when compared with preoperative studies and good blood flow in all vascular structures.

There is the possibility that bacterial infections or reactivation of dormant viral disease occurred with the stress of surgery, immunosuppression, or surgical site contamination, inducing a septic-like condition. The patient received blood products and was exposed to invasive peri-anesthetic procedures (intubation, arterial line, and central venous cannulation, etc.), all of which placed her at risk for an infectious etiology. Sepsis could create an environment where poor hepatic perfusion could predispose the liver to ischemic injury. Our patient, however, did not present with clinical signs of septic shock. Moreover, a sepsis workup evaluating blood, urine, and sputum cultures showed no growth. Fungal and acid-fast bacilli cultures from bronchoalveolar lavages were negative, as were viral serologies for hepatitis A, B, and C, cyclomegalovirus, herpes virus, influenza A/B, and respiratory syncytial virus.

Several diseases involving the liver can result in acute hepatic failure. Wilson's disease is a disorder in copper metabolism and can cause acute liver failure. This carries an extremely high mortality rate with medical management

alone.<sup>2</sup> Autoimmune hepatitis frequently presents insidiously with nonspecific symptoms, but the clinical spectrum is wide, ranging from an asymptomatic presentation to an acute severe disease.<sup>3</sup> Our workup included evaluation of serum ceruloplasmin, serum immunoglobulins, anti-smooth muscle antibodies, and anti-mitochondrial antibodies, all of which were nondiagnostic.

The patient received several hepatotoxic medications prior to the onset of liver failure including sulfamethoxazole/trimethoprim, fluconazole, gancyclovir, and acetaminophen. We were unaware of any herbal medications the patient may have taken at home. With the exception of acetaminophen, most cases of drug induced liver failure present subacutely within 6 months of initiation and carry a poor prognosis.<sup>2</sup> The most common cause of drug induced liver failure, acetaminophen, typically presents hyperacutely and carries a better prognosis than other causes of drug induced failure.<sup>4</sup> Though not used on this patient, a primary hepatic veno-occlusive disorder that is historically associated with renal transplantation occurs secondary to prolonged azathioprine usage. This process involves metabolite-induced injury to the sinusoidal endothelial cells and hepatocytes of zone 3 resulting in progressive narrowing of sinusoidal outflow from cellular debris.<sup>5</sup> Other immunosuppressive agents have been implicated with this disorder; yet, to the best of our knowledge, no documentation of hyperacute liver failure has been published to date. Acetaminophen levels and drugs of abuse panels were unremarkable during our initial investigations.

Once the more common causes of postoperative hepatic failure were ruled out, the focus of our attention shifted toward isoflurane-induced hepatitis. Historically some of the first inhalational anesthetics, chloroform and halothane, were associated with hepatotoxicity secondary to both direct hepatocyte destruction and complex immunologic mechanisms. Halogenated volatile anesthetics, such as halothane, are very lipophilic; thus, a small percentage is metabolized in the liver as opposed to being eliminated via the respiratory system. As a result, oxidative and reductive pathways within hepatocytes are required for their metabolism and subsequent excretion from the body. The primary end product of oxidation, tri-fluoroacetic acid (TFA), forms complexes via binding to specific hepatocyte proteins (Hoptun theory). This reaction stimulates a T cell mediated response against the TFA modified proteins, leading to severe necrotizing hepatitis.

Newer halogenated volatiles, such as isoflurane and sevoflurane, have not been demonstrated to have the same propensity as halothane to cause hepatic dysfunction.<sup>6</sup> It is believed that the decreased incidence of hepatotoxicity is attributed to the newer volatiles utilizing different cytochrome biotransformation pathways. The CYP2E1 pathway that eliminates about 25% of halothane only processes 0.2% of all absorbed isoflurane and 0.02% desflurane. However, because of cytochrome structural similarities, there is still a theoretical risk that oxidative metabolism of any volatile may lead to complexes that can trigger comparable responses as those seen with halothane hepatotoxicity. Liver failure related to volatile anesthetics has been described in patients at the extremes of age, with hepatic failure occurring greater than 48 h after exposure, and presenting

along with other signs of immunologic/allergic reactions.<sup>6,7</sup> Importantly, exposure to one halogenated anesthetic has been associated with cross-sensitivity to other volatile agents.<sup>7</sup>

Our patient, however, presented quite differently than prior cases of isoflurane toxicity. Her hepatic failure manifested less than 24 h after exposure and she did not exhibit any concomitant signs of immunologic/allergic reactions. Classically, the detection of antibodies to TFA proteins was used to make the diagnosis along with clinical features. Unfortunately, we were unable to utilize this testing assay, as it appears that this test is no longer commercially available. Because of this, we were unable to definitively diagnose isoflurane as the primary cause. Despite this, the consensus of our multispecialty team supported isoflurane-induced hepatitis as a diagnosis of exclusion. Our diagnosis was supported by the gross and histological findings at the time of transplant. Histologically, our patient's liver demonstrated centrilobular and bridging necrosis; a finding shared by similar cases of isoflurane-induced hepatitis.

Our management of her liver transplantation and subsequent reoperations centered on the avoidance of inhalational anesthetics and the use of a total intravenous anesthetic. In theory, the removal of her native liver would remove TFA bound proteins and decrease the likelihood of inducing a recurrence of the acute hepatic failure. However

a review of the literature revealed failed to confirm or disprove this opinion.

## Conflicts of interest

The authors declare no conflicts of interest.

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