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Case Report

Hiding in Plain Sight: A Case of Ornithine Transcarbamylase Deficiency Unmasked Post–Liver Transplantation

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Ornithine transcarbamylase deficiency represents the most common inherited defect of the urea cycle. This enzyme, predominantly found in the liver, plays a crucial role in recycling free ammonia, with deficiencies often leading to fatal complications. Here, we present the case of a 63-year-old man with alcoholic cirrhosis who underwent orthotopic liver transplantation, gradual worsening of his mental status, and progressive elevation of ammonia levels. Liver allograft function was deemed normal, raising concern for a donor-derived metabolic disorder of the urea cycle. Evaluation of the donor patient's blood revealed that the donor was heterozygous for the *OTC* gene. Posttransplantation changes in mental status should prompt a clinician to consider the most likely causes; however, once these have been ruled out, it is important to consider the less common causes of metabolic derangements. The rarity of these disorders makes expertise of diagnosis, standardization of evaluation, and treatment strategies challenging.

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KEYWORDS

clinical research/practice; liver transplantation/hepatology; donors and donation: donor evaluation; donors and donation: extended criteria; liver allograft function/dysfunction

Abbreviations

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CRRT, continuous renal replacement therapy; CT, computed tomography; EEG, electroencephalogram/electroencephalographic; HD, hemodialysis; INR, international normalized ratio; IV, intravenous; MELD, Model for End-stage Liver Disease; OTC, ornithine transcarbamylase; UCD, urea cycle disorder

Background

Ornithine transcarbamylase (OTC) deficiency, the most common inherited defect of the urea cycle, has a vast array of clinical presentations, ranging from complete lack of symptoms to cerebral edema and death. OTC functions in the liver to generate citrulline from ornithine and carbamoyl phosphate, thereby recycling free ammonia (1). The intramitochondrial gene encoding for this enzyme is predominantly found in the liver (2). We report on the clinical course of a liver transplant recipient who ultimately died of cerebral edema due to unrecognized OTC deficiency in the donor liver and resultant severe hyperammonemia.

Clinical Case

This is the case of a 63-year-old man with alcoholic cirrhosis and end-stage renal disease who was receiving hemodialysis (HD) and was listed for simultaneous liver–kidney transplantation; he presented to our hospital with worsening hepatic encephalopathy after a fall from his bed. There was no evidence of acute intracranial abnormalities on noncontrast CT scanning of the brain. The Model for End-stage Liver Disease (MELD) score on admission was 39. Spontaneous bacterial peritonitis was ruled out. One of two peripheral blood cultures was positive for methicillin-resistant *Staphylococcus aureus*, so intravenous vancomycin was started after HD. The HD catheter was replaced because of concern for line infection. Transesophageal echocardiographic results were negative for endocarditis, and repeat blood cultures every 48 h over the next 7 days were negative.

The patient underwent deceased-donor orthotopic liver–kidney transplantation (MELD score 38) 10 days after hospitalization, with an intraoperative 4.5-L blood loss requiring the transfusion of 10 U of packed red blood cells, 14 U of fresh frozen plasma, and 4 U of platelets. He was transferred from the operating room to the intensive care unit with hemodynamic instability on a norepinephrine drip at 10 μg/min, the cause of which was thought to be hemorrhagic and hypovolemic shock. His Jackson Pratt drains showed frank blood. Postoperatively, his international normalized ratio (INR) was 2.8, total bilirubin was 7.0 mg/dL, aspartate aminotransferase (AST) was 4414 IU/L, alanine aminotransferase (ALT) was 795 IU/L, and alkaline phosphatase (ALP) was 48 IU/L. With additional fresh frozen plasma transfusions, the bleeding from his Jackson Pratt drains ceased. Also, he was started on continuous renal

replacement therapy (CRRT) for volume overload. Vancomycin was continued, and he was empirically placed on piperacillin-tazobactam, and fluconazole was increased to 200 mg/day intravenous (IV). On postoperative day 1, he remained on norepinephrine at 10 μg/min, and vasopressin at 0.04 units/min was added. Immunosuppression consisted of dexamethasone 100 mg IV, mycophenolate mofetil 500 mg every 12 h, and tacrolimus 1 mg every 12 h. His INR decreased to 1.7, total bilirubin to 14.7 mg/dL, AST to 641 IU/L, ALT to 298 IU/L, and AP to 48 IU/L. He remained intubated and opened eyes to verbal stimuli but did not follow commands. Abdominal ultrasound with Doppler showed a patient hepatic artery.

During the night on postoperative day 1, he experienced generalized body twitching involving the face, head, arms, and legs bilaterally, which was concerning for seizure activity. Repeat head CT scanning showed no evidence of intracranial pathology including cerebral edema. Tacrolimus was held due to concern that this may have been a causative agent (3). The patient's body jerking continued despite the administration of lorazepam, propofol, midazolam, levetiracetam, and phenytoin. A venous ammonia level was checked that night and found to be 1234 μmol/L. Lactulose was started via a nasogastric tube. After being given pentobarbital, the generalized twitching slowed. Pressor requirements were increasing overnight, and on the following day, postoperative day 2, the patient required norepinephrine at 50 μg/min, vasopressin at 0.04 units/min, and phenylephrine initiation. Laboratory results showed INR of 1.5, total bilirubin of 13.5 mg/dL, AST of 307 IU/L, ALT of 213 IU/L, and ALP of 75 IU/L. Repeat ammonia level was 1447 μmol/L.

Our suspicion for primary nonfunction of the liver allograft was low. Thus, our concern was that the extremely high ammonia levels were from a donor-derived metabolic disorder, specifically of the urea cycle. A review of the literature revealed a similar case (1). EEG showed no evidence of clear ictal patterns but showed interference with muscle artifacts, suggestive of myoclonic jerks of nonepileptic type related to anoxic brain injury or critically elevated ammonia levels. After discussion with a genetic specialist, the recommended treatment was IV Ammunol (sodium phenylacetate and sodium benzoate) and HD ultrafiltration. At this time, the patient was being maximized on full pressors and his CRRT was optimized for removal of ammonia. Attempts to get IV Ammunol from an outside hospital were under way. Emergency

retransplantation was considered; however, because of hemodynamic instability and concern for cerebral edema, this was not pursued. Neurologic examination further revealed no response to verbal or tactile stimulation, pupils were fixed with no response to light, there was no withdrawal from painful stimuli, and reflexes were symmetrically and bilaterally suppressed, concerning for the development of cerebral edema. Given the grim prognosis, the patient's family decided to transition the patient to comfort care status and he died soon thereafter.

Further investigation of the donor patient's medical history revealed that the donor was a female college student without known chronic conditions who complained of several days of nausea and headache. She was found unconscious in her dormitory with both deep vein thrombosis and pulmonary embolism. Cross-sectional imaging of her liver revealed no congenital abnormalities including portal vein and hepatic vein shunts. However, there was evidence on magnetic resonance imaging of cerebral edema. Thus, donor whole blood was sent for *OTC* gene sequencing, which revealed that the donor was heterozygous for the *OTC* gene for a variant designated c.274C>G, which results in an amino acid substitution (p.Arg92Gly; glycine substituted for arginine). This variant has been reported to be causative for OTC deficiency (4). The deceased liver recipient underwent autopsy that showed cerebral edema. Histopathological review of tissues from patients who died from UCDs reveals findings that are nonspecific, including normal liver architecture, mild inflammation, cholestasis, gross fatty changes, and frank necrosis (5). Postmortem review of the donor liver in this case showed evidence of coagulative necrosis. The donor family was notified of the OTC deficiency because the donor had two siblings, who were subsequently sent for genetic testing.

Discussion

UCDs are a result of defects or deficiencies in urea synthesis and resultant accumulation of toxic levels of ammonia. The incidence of these disorders approaches nearly 1:30 000–46 000 births. The enzymes that constitute these metabolic pathways are almost exclusively found in the liver, specifically in the periportal hepatocytes. Of the five described entities, OTC deficiency is the form encountered most frequently, with >300 associated mutations identified, the majority of them being missense. OTC is coded by exons 1–10 of the *OTC* gene

on chromosome Xp11.

As seen in our patient, deficiency of the OTC enzyme leads to severely elevated ammonia levels due to accumulation of urea precursors, namely ammonia and glutamine, with resultant toxicity (1). The classic form with neonatal presentation is generally well understood, with symptoms involving cerebral edema causing decreased appetite, lethargy, seizures, and, ultimately, coma; however, a delayed presentation can be seen in those who are partially deficient in the enzyme, leading to symptoms occurring only in adulthood, if at all, and often leading to diagnostic delay (1). Such symptoms could include mental retardation, developmental delay, mood swings, and other nonspecific findings (5). In contrast to the other UCDs, which have autosomal recessive transmission, OTC deficiency is X-linked and, thus, expectedly, its classic presentation is predominantly seen in males. Heterozygous females, however, have varying presentations in disease severity due to lyonization, or random X-chromosome inactivation during development, and presentation can range from absence of symptoms to fatal complications (6). It is thought that 15–20% of females ultimately develop symptoms (1). Individuals with minimal expression of the mutations can have clinically silent disease until encountering a stressor, tipping the body into a catabolic state and thus unmasking the disease process. Such states could include severe infection, surgical intervention as in our transplanted patient, or high dietary protein intake (7).

The long-term therapeutic approach to UCDs focuses on decreasing production of and increasing elimination of nitrogenous wastes via dietary protein restriction, arginine supplementation, and sodium benzoate to help remove ammonia (8). In the acute setting, treatment involves arginine and nitrogen scavenger administration in conjunction with HD and maintenance of hypothermia. Hypothermia has been shown to abrogate many of the effects of ammonia such as free radical production, astrocyte swelling, and inflammation and helps to slow protein catabolism and production of ammonia (9).

In the posttransplantation setting, acute changes in mental status generally focus on the most likely causes such as metabolic abnormalities, infections, drug reactions, and central nervous system vascular events. In this particular case, serial monitoring of the ammonia level aided in determining the most likely cause of the patient's clinical deterioration. Donor-derived UCDs, with OTC

deficiency being the most common, should be included in the differential diagnosis of posttransplantation hyperammonemia in addition to impaired liver function and primary nonfunction of the allograft (10). Though not assessed in our patient, elevated urinary orotic acid also helps to support the diagnosis of a UCD and aids in distinguishing between the various forms, with extreme elevation in OTC deficiency (1). It is our belief that the postoperative course in this case was caused by acute hyperammonemic crisis from OTC deficiency with organ transplantation as the catabolic trigger (11).

The extreme hyperammonemia and declining mentation in the setting of improving graft function and lack of portosystemic shunts in our patient should have alerted the transplant team sooner. Urgent re-transplantation is an approach to be considered in the setting of hyperammonemia to this degree; however, a patient's neurological status needs to be determined with consideration of intracranial pressure monitoring. The donor history of nausea, vomiting, and headache coupled with imaging evidence of cerebral edema without trauma should have raised concern about the possibility of unrecognized OTC deficiency. However, the patient also had a pulmonary embolism, which was reported to be the primary cause of death. After the fact, the donor history was somewhat vague, but a more thorough evaluation of the donor at the time of death could have prevented donation of the liver. There was no examination for papilledema reported, and it did not appear that a lumbar puncture was entertained early in the course. Serum ammonia levels were not checked in the donor. Significant hyperammonemia detected in the donor would have also been a red flag to forgo donation. The rarity and underrecognition of UCDs also make exclusion of organ transplantation problematic. In retrospect, at the time the organ was offered and accepted, further workup and investigation into the donor history could have prevented donation.

This serves as a learning opportunity. The rarity of these disorders makes diagnosis and treatment difficult. Specifically with OTC deficiency, it has been found that the same genetic defect can have varying degrees of presentation within the same family, further highlighting the unpredictability of the disease process. Routine screening for UCDs is currently not a part of standard pretransplantation evaluation. Additionally, there is no rapid testing available even when the diagnosis is suspected. A high index of clinical suspicion from

both the organ donation team and the transplant team remains the best method of avoiding this complication in patients undergoing liver donation.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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