CASE REPORT

Plasmapheresis for hyperbilirubinemia and bile cast nephropathy after terbinafine therapy

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ABSTRACT

We report a 62-year-old Caucasian female who was treated with plasmapheresis for hyperbilirubinemia that was triggered by cholestatic liver injury that likely developed from terbinafine therapy. She initially presented with fatigue, pruritus, and jaundice. Her peak serum total bilirubin level was 66.5 mg/dL. She also had an acute kidney injury with an initial urinalysis that showed 30 proteins, 4+ bilirubin, 0-2 red blood cells, 0-5 white blood cells, 0-2 hyaline casts, and 3-5 granular casts with suspicion for bile cast nephropathy. During her hospitalization, hemodialysis and plasmapheresis were performed, and her total bilirubin decreased to 3.1 mg/dL at the time of transfer to another facility about two months after her initial presentation.

INTRODUCTION

Drug-induced cholestasis is a rare form of liver injury. The pathophysiology is poorly understood but typically results in dysfunction of bile formation and subsequent hepatocellular dysfunction.[1] Furthermore, the presentation itself is rare, as cholestasis causes about 2-5% of drug-induced liver injury and jaundice in hospitalized patients.[2-5] Terbinafine is a synthetic fungicidal agent. Under the FDA drug-induced liver injury (DILI) classification, terbinafine is in the "most-DILI-concern" category.[6] Ultimately, cholestasis and bile acid products can lead to systemic manifestations and organ injury. Common manifestations include pruritus, jaundice, nausea, malaise, anorexia, and abdominal pain. In severe cases, organ injury may include hepatitis, bile duct scarring, or kidney injury.

Kidney injury from excessive bile acids, also known as bile cast nephropathy, has been described in the presence of hyperbilirubinemia and kidney injury without another explanation.[7] Often, bile acids are seen on renal biopsy. Therapeutic plasma exchange (TPE) to lower serum bile acids has been reported in patients who are

refractory to medical therapy.[8-9] We describe a case of severe cholestasis likely due to terbinafine that led to liver injury, acute kidney failure, and sepsis. Notably, dialysis and TPE were used to support her kidneys and remove bilirubin.

CASE PRESENTATION

A 62-year-old Caucasian female with history of type 2 diabetes mellitus, hypertension, hypothyroidism, and post-traumatic stress disorder (PTSD) was hospitalized for cholestatic liver injury after presenting with one month of fatigue, decreased appetite, 20-pound weight loss, nausea, pruritus, and yellowing of her skin. About 5 weeks prior, she started taking terbinafine 250 mg daily for a fungal infection of the toe. She noticed skin yellowing 1 week prior to presentation and stopped the medication. She had no history of autoimmune disease or cirrhosis in her medical and family history and denied alcohol, tobacco, or recreational drug use. Additional home medications included bupropion, empagliflozin, metformin, levothyroxine, risperidone, and sertraline, all of which are in the less/no-DILI concern category or not listed.

Initial labs were significant for aspartate aminotransferase (AST) 139 U/L, alanine transaminase (ALT) 230 U/L, alkaline phosphatase (ALP) 1542 U/L , total bilirubin 44.3 mg/dL, direct bilirubin 30.8 mg/dL, white blood cells 1.89 K/uL, red blood cells 2.78 M/uL, hemoglobin 7.0 g/dL, platelets 97 K/uL, creatinine 1.6 mg/dL, sodium 137 mmol/L, potassium 4.1 mmol/L, chloride 111 mmol/L, CO2 18 mmol/L, and calcium 7.1 mg/dL. The R-value of liver injury was 0.58, consistent with cholestatic hepatocellular injury. Thorough infectious and autoimmune evaluations were negative. Initial imaging on admission included a CT abdomen and pelvis, abdominal ultrasound, and MRI abdomen which demonstrated gallbladder wall thickening without gallstones, portal hypertension, and an enlarged liver without evidence of parenchymal infection or frank cirrhosis. She subsequently underwent a liver biopsy three days after presentation that revealed extensive cholestasis without extrahepatic obstruction consistent with toxin or drug-induced liver injury. Pancytopenia continued to worsen, and a bone marrow biopsy one week after presentation showed hematopoiesis and lymphohistiocytic aggregates that were nonspecific. Two weeks after her initial presentation, her total bilirubin was 66.5 mg/dL, ALP 1,852 U/L, and creatinine 3.71 mg/dL, and she was transferred to our facility for liver transplant evaluation.

Symptoms on initial presentation at our facility included nausea, pruritus, bilateral lower extremity edema, and jaundice. Mentation was appropriate throughout her hospitalization. Hepatology was consulted for liver transplant assessment and cholestatic liver injury. She was not deemed a liver transplant candidate given the expectation that she could recover from presumed DILI. Vitamin K and ursodiol were administered. Hematology was consulted for pancytopenia and judged that this was most likely marrow suppression in the setting of liver dysfunction.

Nephrology was consulted to evaluate her worsening acute kidney injury (AKI). Initial fractional excretion of urea suggested an intrinsic etiology. Initial urinalysis with microscopy showed 30 proteins, 4+ bilirubin, 0-2 red blood cells, 0-5 white blood cells, 0-2 hyaline casts, and 3-5 granular casts. Bile cast nephropathy was suspected based on granular casts seen on urinalysis with microscopy. Renal biopsy for definitive diagnosis was not conducted due to concerns about bleeding risk with thrombocytopenia. Attempts to improve renal function in the setting of liver injury

were initiated with octreotide, albumin, and midodrine with no significant response. Hemodialysis was subsequently initiated on hospital day 6 at our facility. Due to suspected contribution of bile cast nephropathy to her kidney injury, TPE was initiated on hospital day 11 with a goal to decrease total bilirubin. TPE was performed via automated centrifugal apheresis using a one-plasma volume exchange and 5% albumin as the replacement fluid for each procedure. In the days following the initiation of TPE, creatinine remained relatively unchanged, though creatinine was not able to be measured from hospital day 1-13 due to icterus in the lab samples. Creatinine continued to rise and fall throughout her hospitalization (Figure 1). Her urine output, however, increased.

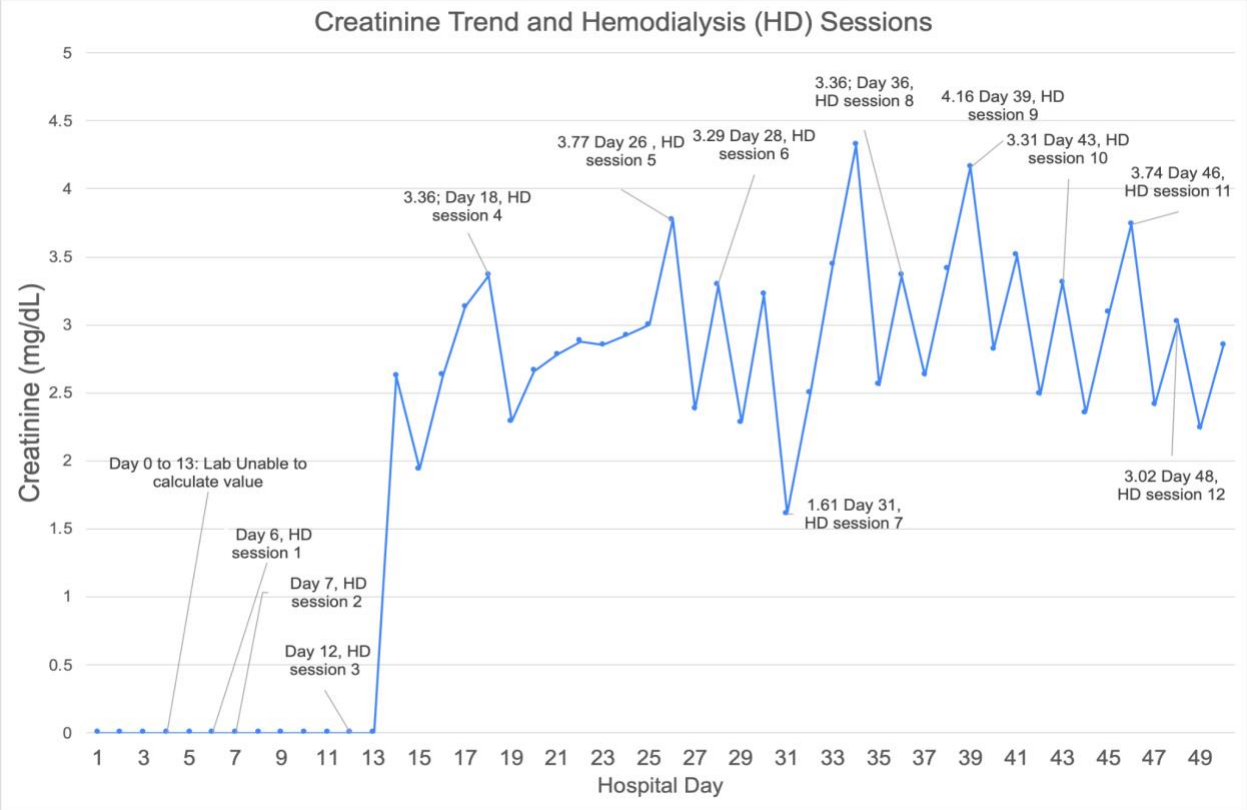

Figure 1. Creatinine trend and hemodialysis session days

Notable in her hospital course was a significant uptrend in liver enzymes, decreasing urine output, and worsening nausea on hospital day 21. Subsequent right upper quadrant ultrasound showed a thickened gallbladder wall, and MRCP showed evidence of portal hypertension. Liver fibroscan on hospital day 27 showed increasing liver stiffness and liver transplant workup was initiated with incidental findings of *Klebsiella* bacteremia and pericardial effusion on transthoracic echocardiogram. *Klebsiella* bacteremia was treated with meropenem and hemodialysis line replacement, and pericardial effusion was treated with pericardiocentesis and pericardial drain. No blood cultures had been drawn prior to this event. AST and ALT

improved, urine output increased with treatment of infection, and transplant evaluation was held again.

Figure 2 outlines total bilirubin levels during her hospital course. After three TPEs, her total bilirubin level was 24.4 mg/dL. She received three more TPEs during the following week, and her total bilirubin decreased to 15 mg/dL. Her total bilirubin continued to decrease each day without additional TPEs to a level of 3.1 mg/dL on the day of transfer, as she was deemed stable enough for transfer to a facility closer to her home on hospital day 50.

Signs of clinical improvement prior to her transfer included increased urinary output and improvement in nausea, vomiting, and per os (PO) tolerance that allowed her to be advanced to a solid diet. Unfortunately, she was lost to follow up and further outcomes were unavailable.

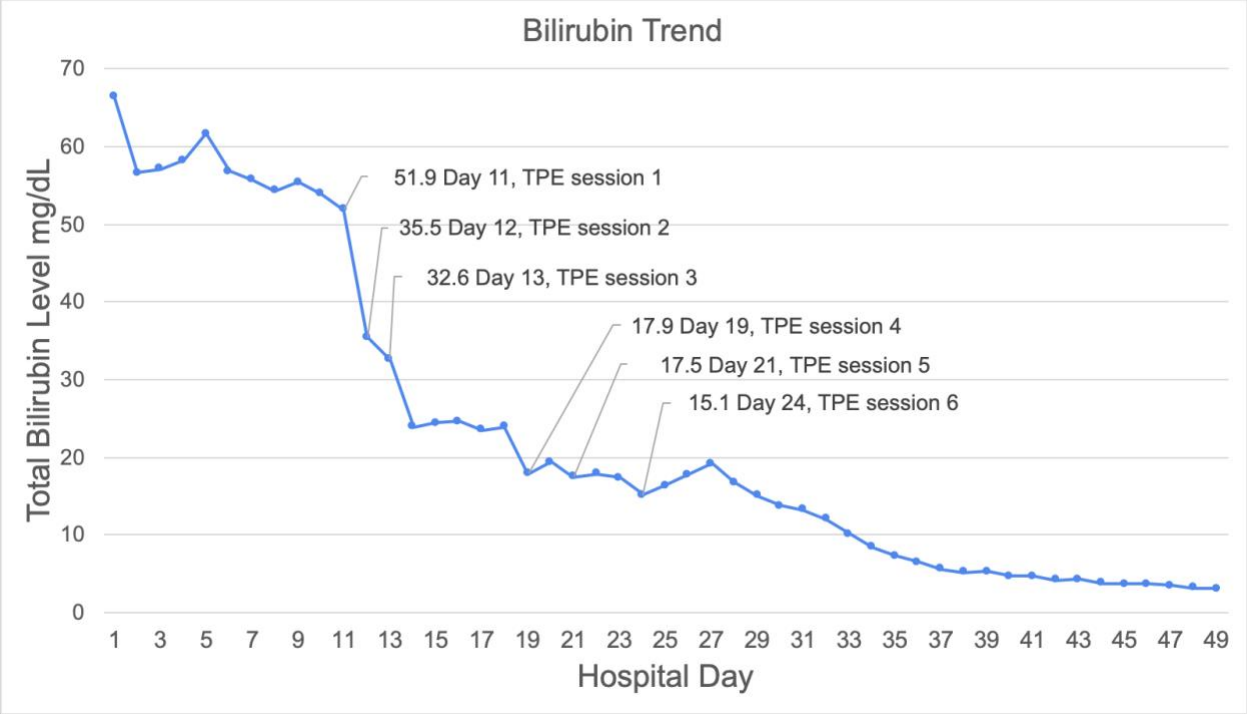

Figure 2. Patient's bilirubin trend and days of therapeutic plasma exchange (TPE).

DISCUSSION

We present a case of bile cast nephropathy in the setting of severe hyperbilirubinemia caused by cholestatic liver injury. Terbinafine was the likely etiology of livery injury with a Roussel Uclaf Causality Assessment Method (RUCAM) score of 8 corresponding to high probability.[10] Hyperbilirubinemia seemed to improve with TPE; however, her kidney injury was slow to recover despite the reduction in bilirubin. Hemodialysis was initiated during hospitalization and was ongoing at the time of transfer.

TPE is an extracorporeal technique for removing large molecular weight substances from blood. The typical criteria needed for a substance to be significantly removed through TPE include: size over 15,000d, relatively low volume of distribution that makes it bioavailable in the

blood, long half-life that allows for an effective period of decreased serum concentration of the substance, and the substance should be acutely toxic with failed removal attempts/lack of other removal methods.[11]

One of the earliest reports of a causal relationship between jaundice and kidney injury was made by Haessler et al. in 1922, who reported that "bile-stained urinary sediment is a regular accompaniment of marked jaundice."[12] Bile cast nephropathy, also known as cholemic nephropathy, is a condition in which renal dysfunction occurs in the setting of liver injury. In most cases described, the types of liver injuries typically associated with bile cast nephropathy include obstructive jaundice, drug-induced liver injury, acute hepatitis, and malignancy. Typically, total bilirubin levels are above 20 mg/dL for bile cast nephropathy to occur.[12] The mechanism of renal dysfunction is likely multifactorial. The first component is the oxidative stress that bilirubin adds to kidney tubules. With increased bilirubin levels, there is an increased risk of oxidative damage to renal structures. From a mitochondrial perspective, there is evidence that hyperbilirubinemia can lead to the uncoupling of oxidative phosphorylation that then impairs ATP production in the mitochondria. The renal tubules depend on multiple ATP-driven pumps to maintain pH.[13]

Bile cast nephropathy is likely underdiagnosed. The gold standard for diagnosing bile cast nephropathy is renal biopsy. However, when liver injury is severe enough to impair hemostasis, the bleeding risk from renal biopsy often outweighs the benefit of a definitive diagnosis.[14] For these reasons, there is limited documentation of the disease course and treatment of bile cast nephropathy. Slambrouck et al. conducted one of the larger scale studies with a clinicopathologic study of 44 jaundiced patients and found that 24 patients had bile casts.[15] Due to the complexity of kidney biopsy interpretation, bile cast nephropathy is typically diagnosed clinically after other causes of AKI have been ruled out. Common urinalysis findings in bile cast nephropathy include bile acid and granular casts, as seen in this patient.

The underlying goal of bile cast nephropathy treatment is correcting hyperbilirubinemia. When refractory to traditional bile acid lowering therapies such as ursodeoxycholic acid, cholestyramine, or other bile resins, hemodialysis and TPE have been utilized. The ideal TPE schedule is unclear. Table 1 summarizes prior case reports that used TPE in patients for whom renal failure was a concern.[9,16,17] In 2 of 3 cases, the patient made a full renal recovery, though the long-term impact on the kidneys remained unclear. The third patient required dual liver-kidney transplantation when renal recovery was not realized despite several TPEs. Our case demonstrates another mixed outcome of TPE. While the patient's total bilirubin continued to decline and urine output improved, creatinine did not significantly change, and she remained on hemodialysis at the time of transfer.

TPE has also been used for high bilirubin/bile salt levels due to intrahepatic cholestasis of pregnancy (ICP). In four reported cases of using TPE for refractory pruritus in patients with ICP and elevated bile acids, TPE inconsistently changed both pruritus and bile acid levels.[18-20] All patients delivered early and never had renal compromise. In the cases for both pregnant patients and those with kidney injury utilizing TPE for hyperbilirubinemia, there was no clear pattern to the frequency of TPE and trends of bilirubin. Some cases utilized daily TPE for a few days, while others had several days in between. In our case, we generally used a TPE schedule of once every 1-3 days to allow for re-equilibration

between the tissue and blood compartments in the days between TPEs. Although the evidence mainly consists of sparse uncontrolled observational reports, the American Society for Apheresis reported an overall response rate of 77% among patients with pruritus due to hepatobiliary disease.[21]

In conclusion, elevated bile acids can cause symptoms and organ damage ranging from pruritus and jaundice to kidney injury and kidney failure. It is plausible that TPE may be effective in decreasing total bilirubin levels when more conservative measures fail. Overall, it is unclear if TPE leads to kidney recovery. Our patient demonstrated some initial improvement in renal function such as increased urine output. The complications that followed including infection likely played a role in the acute worsening seen in the second half of her hospital course after the TPE series. Controlled trials are needed in this area. While TPE may treat hyperbilirubinemia in refractory patients, treating hyperbilirubinemia may not guarantee a significant improvement in renal function.

Table 1: Review of previous reports on TPE for hyperbilirubinemia and kidney injury

	Total Bilirubin level prior to TPE initiation (mg/dL)	Total bilirubin following last TPE (mg/dL)	Number of TPEs	TPE frequency	Renal function following TPE completion
Ocon (2019)	49.5	6.9	5	Daily	Creatinine 0.9 mg/dL, producing adequate urine
Patel (2016)	25.3	10.9	Unspecified	Daily followed by PRN	Rebound worsening creatinine and bilirubin requiring Liver/Kidney transplant
Flores (2016)	44.6	14.4	5	Unspecified	Creatinine 1.3 mg/dL, producing adequate urine

Notes

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