CASE REPORT

Efficacy of extracorporeal albumin dialysis for acute kidney injury due to cholestatic jaundice nephrotoxicity

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SUMMARY

We report a case of a 37-year-old man with Maturity Onset Diabetes of the Youth (MODY) type 5, admitted for an episode of cholestasis and a simultaneous acute kidney injury (AKI). Chronic liver disease was due to a mutation in the *transcription factor 2* (*TCF2*) gene, thus highlighting the need for a close liver follow-up in these patients. AKI was attributed to a cholemic nephropathy based on the following rationale: (1) alternative diagnoses were actively ruled out; (2) the onset of AKI coincided with the onset of severe hyperbilirubinaemia; (3) renal pathology showed large bile tubular casts and a marked tubular necrosis and (4) creatinine serum dramatically decreased when bilirubin levels improved after the first sessions of extracorporeal albumin dialysis (ECAD), thus suggesting its role in renal recovery. Even though cholestasis can precipitate renal injury, the diagnosis of cholemic nephropathy could require a renal biopsy at times. Future studies should confirm the benefits of ECAD in cholemic nephropathy.

BACKGROUND

Acute kidney injuries (AKI) in patients with severe jaundice have often been reported.^{1,2} This has led the medical community to consider cholestasis as a cause of renal failure, and to classify this mechanism of injury under the term, 'cholemic nephropathy'. However, reports addressing renal histopathological changes in patients with increased concentrations of bile salts are limited;^{3,4} the lack of specific therapeutic options also remains an important limitation for clinical management.

We report a case of a 37-year-old man presenting with Maturity Onset Diabetes of the Youth (MODY) type 5 admitted with acute cholestasis and onset of AKI. When taken together, the patient's history, biochemical results, renal histology and the AKI recovery during sessions of extracorporeal albumin dialysis (ECAD) strongly suggest a diagnosis of cholemic nephropathy. The transient renal recovery observed during ECAD sessions highlights the need for further evaluation of this technique in terms of efficacy and benefits.

CASE PRESENTATION

A 37-year-old man had suffered from MODY 5 diabetes since the age of 15 years. The mutation identified was a heterozygous missense mutation in the *transcription factor 2* (*TCF2*) gene (PArg235Trp). His two comorbidities were a stable chronic kidney disease stage 2 (plasma creatinine 116 µmol/L,

estimated glomerular filtration rate 69 mL/min per 1.73 m² using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula) and a moderate but stable hepatic impairment (cytolysis and cholestasis) since the age of 24 years (70 UI/L serum glutamic oxaloacetic transaminase (SGOT), 150 UI/L serum glutamic-pyruvic transaminase (SGPT), 1000 UI/L γ-glutamyl-transferase (GGT), 300 UI/L alkaline phosphatase, normal bilirubin levels), attributed to the *TCF2* mutation. Indeed, autoimmune, viral, alcoholic, anatomic, metabolic (ceruloplasmin, α-1-antitrypsin and ferritin) and endocrinological aetiologies were ruled out to explain his liver dysfunction; three liver biopsies (performed at 26, 28 and 35 years) showed a biliary duct dystrophy with a chronic cholangiopathy, but without steatosis, all these findings being consistent with a *TCF2* phenotype. The treatment was limited to insulin therapy. The mutation carrier, namely the patient's father, was also diabetic; he displayed similar unexplained chronic liver disorders and cystic renal dysplasia.

The patient presented a sudden alteration of his clinical status in the context of the onset of jaundice and pruritus (day 1). He was hospitalised on day 21. At the time of admission, laboratory findings showed hyperbilirubinaemia (344 µmol/L), mostly conjugated (260 µmol/L), and AKI, classified as 'injury' according to the RIFLE (Risk-Injury-Failure-Loss of function-ESRD) criteria:⁵ plasma creatinine was 214 µmol/L (enzymatic isotope dilution mass spectrometry (IDMS) method assay) with preserved urine output (1.5 L). The patient displayed a mild proteinuria (0.36 g/24 hours), with neither haematuria nor leucocyturia (<2/mm³). His chronic cytolysis was stable (714 UI/L SGOT, 75 UI/L SGPT).

INVESTIGATIONS

Renal ultrasounds showed well-differentiated small-sized kidneys (10 and 10.5 cm). There were no clinical or biological symptoms of dehydration nor of hepatorenal syndrome. Autoimmune, infectious, metabolic and monoclonal aetiologies of cholestasis and AKI were actively ruled out (table 1).

An endoscopic ultrasound of the upper digestive system revealed biliary sludge. A liver biopsy was performed on day 23 (figure 1), still suggesting a non-specific chronic cholangiopathy with ductopaenia.

The AKI and icteric cholestasis rapidly worsened (creatinine 520 µmol/L, bilirubin 403 µmol/L,

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Table 1 Investigations performed to rule out other aetiologies

Laboratory testing	
Autoimmunity	C reactive protein, complement system proteins (component 3 and 4) and hemolytic complement activity; cryoglobulinaemia; antinuclear antibodies; antiactin antibodies; antimitochondrial antibodies; ANCA; anticardiolipin antibodies; rheumatoid factor; antiendoplasmic reticulum antibodies
Virology	Hepatitis A, B, C and E virus; <i>Herpes simplex virus 1</i> and <i>2</i> ; <i>Cytomegalovirus</i> ; Epstein-Barr virus; Varicella-zoster virus; human T-Lymphotropic virus 1 and 2; Parvovirus; <i>Cytomegalovirus</i> PCR
Bacteriology	Multiple blood cultures; <i>Leptospira</i> ; <i>Mycoplasma</i> ; <i>Brucella</i> ; <i>Legionella</i>
Toxicology	Large negative testing
Metabolic diseases	Ceruloplasmin; serum and urine copper; ferritin, transferrin saturation coefficient, serum iron
Neoplasia	Serum-free light chains; serum immunoelectrophoresis
Imaging and biopsies	
Upper gastrointestinal endoscopy and biopsies	
Digestive echoendoscopy	
Liver ultrasound	
MR cholangiography	
Functional hepatic MRI	
Abdominopelvic scannography	
Transoesophageal echocardiography	
Renal ultrasounds	
ANCA, antineutrophil cytoplasmic antibodies.	

figure 2). A first renal biopsy was performed on the left kidney on day 38, revealing a global and diffuse acute tubular necrosis, with granular casts and an overload of epithelial pigmentation, thus suggesting bilirubin nephrotoxicity. No glomerular deposit was visible by immunofluorescence microscopy (figure 3A, B).

TREATMENT

Owing to this severe AKI attributed to icteric cholestasis, the patient was transferred to an intensive care unit on day 41, where he initially received a vascular expansion (6 L of isotonic saline solution), without evident results other than haemodilution: creatinine, haematocrit and protein were all decreased, respectively, from 520 to 444 $\mu\text{mol/L}$ (figure 2), 24.2–19.4% and 58–51 g/L. The diuresis was maintained between 3 and 5 L/day.

In order to decrease the hyperbilirubinaemia and limit its nephrotoxicity, the patient received nine ECAD sessions: one with molecular adsorbent recirculating system (MARS) and eight with technical single-pass albumin dialysis (SPAD). The vascular expansion was stopped. His hydration status remained clinically stable during this period, with a total weight loss of 3 kg between day 41 and 50, attributed mainly to poor intake. The first four sessions, from day 41 to 44, lowered the bilirubin level from 480 to 172 $\mu\text{mol/L}$. The diuresis was preserved above 2000 mL/day for these 4 days, and serum creatinine decreased from 444 to 248 $\mu\text{mol/L}$ without requiring haemodialysis. We therefore concluded that this was a partially AKI recovery.

Figure 1 Liver biopsy performed at the beginning of present history showing intrahepatic cholestasis (bile overload in hepatocytes and liver sinusoids) without biliary canaliculi dilatations (H&E saffron stain, light microscopy, $\times 400$).

OUTCOME AND FOLLOW-UP

Unfortunately, the patient developed a pelvic haematoma on day 45, requiring contrast studies, followed up by an episode of *Staphylococcus aureus* sepsis on day 50. Despite continuing ECAD, his bilirubin levels rebounded to their initial values, without other hepatic laboratory abnormalities. At day 52, the liver biomarkers were: 507 $\mu\text{mol/L}$ total bilirubin, and 55 UI/L SGOT, 51 UI/L SGPT, 70 UI/L GGT and 113 UI/L alkaline phosphatase. In this period he became irreversibly anuric, and intermittent haemodialysis was initiated while ECAD was withdrawn.

A second renal biopsy was performed on the left kidney on day 67, for possible combined liver–kidney transplantation. Results showed an important worsening of the acute tubular necrosis, with considerable bilirubin deposits and interstitial fibrosis (25–30%), with no mitosis in the tubular epithelium, suggesting a worsening bilirubin nephrotoxicity.

Thus, the patient underwent a simultaneous liver–kidney transplantation on day 73. During the postoperative period, his liver status rapidly improved, with a rapid decrease of bilirubin

Figure 2 Plasma creatinine and bilirubin evolution during the first 40 days of hospitalisation. Temporal variations in plasma bilirubin and creatinine levels (in $\mu\text{mol/L}$) prior to and following liver dialysis sessions (blue arrows). Day 1 was considered when clinical presentation began.

Figure 3 Kidney biopsy performed on day 38 (H&E saffron stain, light microscopy). (A) Signs of acute tubular injury: dilated tubules with flattened epithelium. We identify greenish-brown intraluminal casts (H&E saffron stain, light microscopy, $\times 400$). (B) Severe swelling of tubular cells. Note intraepithelial brown vacuoles and intraluminal casts (bile acid casts) (H&E saffron stain, light microscopy, $\times 7000$).

level. The diuresis improved 15 days after transplantation, as the bilirubin level dropped below $100 \mu\text{mol/L}$. The intermittent haemodialysis was stopped 44 days after the transplantation. Renal function then stabilised: creatinine serum $110 \mu\text{mol/L}$, CKD-EPI $73 \text{ mL/min/1.73 m}^2$.

Three years after the transplantation, the patient still displays stable kidney and liver functions.

DISCUSSION

We report on the case of a 37-year-old man who presented with AKI attributable to bilirubin tubular toxicity. Temporary renal recovery was observed in response to improved bilirubin levels obtained with ECAD, but concomitant events (ie, contrast media injection and vancomycin toxicity) impaired residual renal function. This case report strongly suggests the need to stabilise hyperbilirubinaemia in patients with AKI linked to acute liver failure and, when required, to use ECAD (MARS or SPAD systems).

This patient's medical history included MODY 5 diabetes, stage 2 CKD and biological liver disorders with an anatomic ductopaenia. The affected gene in MODY 5, namely *TCF2*, encodes the hepatocyte nuclear factor-1 β (HNF1- β), a transcription factor of the utmost importance for the expression of various genes in the kidney, intestine, pancreatic islets and liver cells.^{6,7} Pancreatic dysgenesis leads to a reduction of β -cells and, subsequently, to deficient insulin secretion. *TCF2* mutation is

also known to be associated with kidney cysts and renal dysplasia,⁸ but not with cholemic nephropathy, as observed in our patient. Mice with homozygous deficiency of HNF1- β present with a ductopaenia and a bile duct dysplasia,⁹ similarly to what we observed on our patient's biopsies. However, very few patients with *TCF2* mutations have been described with liver dysfunction and biliary manifestations,^{10,11} or with anatomic liver pathology.¹² In our patient, the role of the *TCF2* mutation in his liver disorder was suggested by the history of liver disorders in the family mutation carrier, by the ductopaenia observed on liver biopsies and by the negativity of exhaustive aetiological investigations. However, the exact trigger and aetiology of the acute cholestasis are unknown.

AKI in deeply jaundiced patients have often been reported.^{1,2} This has led scientists to consider cholestasis as a cause of renal failure, and to classify this mechanism of injury under the term, 'cholemic nephropathy'. This unspecific term covers impaired renal functions in patients with cholestasis with histomorphological changes, including the formation of intratubular casts and tubular epithelial cell injuries.^{1-4,13} However, few data exist about renal histopathological changes in humans with isolated bilirubin increase. The underlying mechanisms of cholemic nephropathy remain unclear. Different pathophysiological mechanisms are plausible: it could be due to (1) an alteration of the systemic circulation (due to the haemodynamic consequences of liver dysfunction and portal hypertension: an intravascular volume depletion, a peripheral vasoplegia^{14,15} and an impaired cardiac performance^{16,17}); (2) a renal vascular alteration (characterised by an afferent arterial vasoconstriction,¹⁸ and triggered by an inadequate effective circulatory volume and a renin-angiotensin-aldosterone activation) and (3) the formation of intratubular bile casts and the direct bilirubin tubular toxicity.³ This latter mechanism could occur mainly in case of prolonged exposure to high levels of bilirubin, which are typically $>340 \mu\text{mol/L}$. If the liver injury improves, it is important to keep in mind that the recovery of the renal function can be delayed, depending on the extent of proximal tubulopathy and the formation of bile casts.²

In this report, the AKI was linked to the presence of hyperbilirubinaemia: (1) alternative diagnoses, such as sepsis, heart failure, hepatorenal syndrome, drug-related nephrotoxicity and IgA nephritis, were actively ruled out; (2) the development of AKI strikingly coincided with the appearance of hyperbilirubinaemia; (3) renal pathology demonstrated the presence of large epithelial bile casts in the lumen of distal tubules and the cytoplasm of proximal tubules, along with a marked tubular necrosis, consistent with previously published data and (4) a significant creatinine decrease was observed when bilirubin levels decreased after the first ECAD sessions. Interestingly, as creatinine assays used in our laboratory were based on an IDMS enzymatic method, hyperbilirubinaemia values did not interfere with the results of creatinine values. Unfortunately, during the patient's hospitalisation in the intensive care unit, the evolution of proteinuria, microhaematuria and tubular epithelial cell casts in urine sediment analysis were not screened to corroborate our hypothesis of acute tubular necrosis recovery.

The aim of ECAD is to reduce endogenous albumin-bound toxins accumulated during liver failure. The two methods used in this case report, namely the MARS and SPAD techniques, proved their feasibility and efficacy¹⁹⁻²¹ to reduce bilirubin levels in plasma to a similar extent.²² MARS and SPAD have been reported in patients with an acute-on-chronic or acute liver failure and/or with pruritus or intoxication;²³⁻²⁵ if required, these two techniques can be coupled to conventional haemodialysis or continuous renal replacement therapies. A

third non-cell-based liver support technique is also available to perform hepatic detoxification, namely the fractionated plasma separation, adsorption and haemodialysis (Prometheus). This system consists of two circuits: one for conventional high-flux haemodialysis, and one module for protein-bound substances depuration.²⁶ However, although it appears to be a technology with few side effects and satisfactory performance,^{26–27} the available evidence remains poor.²⁸ Moreover, this technique was not available in our unit.

To the best of our knowledge, the use of ECAD to treat isolated hyperbilirubinaemia without hepatocellular impairment has only been described in one patient.²⁹ MARS, unlike SPAD, may affect other biological parameters, such as creatinine and urea.²² Based on the published data, the clearance of the creatinine is, however, moderate (–24 µmol/L/MARS session for a dialysate flow of 2 L/hour). It was probably even lower during our patient's single MARS session, because of the lower dialysate flow used (1 L/hour). Thus, the reduction of the creatinine level observed when our patient was treated with ECAD is not attributable to an elimination of the creatinine by the technique, but rather to an improvement of the renal function secondary to the decrease of the bilirubin level.

Patient's perspective

During the first liver dialysis session, I felt a great relief on toxins elimination.

Learning points

- The need for close liver follow-up in patients presenting with MODY 5 diabetes.
- The necessity to evoke the diagnosis of cholemic nephropathy in patients with cholestasis, and to confirm it as often as possible with a kidney biopsy.
- The urgent need for further evaluation of extracorporeal albumin dialysis in cholestatic jaundice with complications, such as cholemic nephropathy.

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