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CASE REPORT

Renal Recovery Following Orthotopic Liver Transplant after Prolonged Kidney Injury: Perspectives on Diagnosing Hepatorenal Syndrome and Determining Which Patients Should Undergo Simultaneous Liver–Kidney Transplantation

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Abstract

We present a case of an individual with cirrhosis and renal failure. This case is notable because the patient was found to have hepatorenal syndrome (HRS) superimposed on Immunoglobulin A (IgA) nephropathy. After 8 months of dialysis, the patient had significant renal recovery following orthotopic liver transplant (OLT). Cases such as this are not likely to be rare, as case series have shown that IgA deposits are a common occurrence in patients with cirrhosis, including those who have HRS. While current diagnostic criteria for HRS emphasize the importance of excluding glomerular lesions, we argue that this approach should be reconsidered. More specifically, we feel that the diagnostic approach to HRS should be more inclusive of cases in which patients have simultaneous HRS and glomerular injury. In addition, our case highlights the challenges in determining which patients will benefit most from simultaneous liver–kidney transplants over OLTs alone.

Keywords: hepatorenal syndrome; liver cirrhosis; organ allocation; simultaneous liver–kidney transplantation; treatment outcome

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Introduction

Kidney injury in the setting of cirrhosis is a common phenomenon. A number of different renal pathologies are commonly associated with liver disease, including Immunoglobulin A (IgA) nephropathy, cryoglobulinemia, membranous nephropathy, membranoproliferative glomerulonephritis, and hepatorenal syndrome (HRS) (1–3). For treating kidney disease, a number of treatment options exist, which vary based on the cause of the kidney injury. Orthotopic liver transplant (OLT) has been well described as a definitive treatment in some cases of HRS (4). Our understanding of why some patients with HRS recover renal function after OLT and why others do not is limited; however, some data suggest that duration of kidney injury prior to transplant is an important factor (5). Duration of injury is a plausible factor, as it is well appreciated that the common final pathway for all kidney injury, irrespective of initial etiology, is diffuse, irreversible fibrosis (6).

Therefore, it is reasonable to speculate that during prolonged courses of HRS, the injury transforms from a functional change in renal function to an irreversible injury on the pathway to fibrosis. However, it is unclear what specific factors dictate the timing of this transformation in HRS. Therefore, significant challenges exist regarding the prediction of whether a given individual will actually recover renal function after OLT or not, as there is likely to be significant heterogeneity with respect to the time it takes to develop irreversible kidney injury among subjects with HRS. Under the current Organ Procurement and Transplantation Network (OPTN) policy, adult candidates seeking simultaneous liver–kidney transplantation (SLK) must meet one of the following medical eligibility criteria: (i) presence of chronic kidney disease (CKD) defined as a glomerular filtration rate (GFR) <60 mL/min for ≥90 days *and* either on dialysis as an end-stage renal disease (ESRD) patient or a creatinine clearance (CrCl) or estimated glomerular filtration rate (eGFR) of ≤30 mL/min at the time of kidney transplant listing, (ii) sustained acute kidney injury (AKI) defined as a CrCl or eGFR ≤25 mL/min or dialysis dependence lasting for at least 6 weeks, or (iii) one of several metabolic diseases (7). The appropriateness of these criteria has been under debate since it was adopted in 2016 (8, 9). In this article, we report a case of a patient with ESRD in the setting of liver cirrhosis from alpha-1 antitrypsin deficiency (A1ATD) who recovered renal function following OLT. Our case is notable as the subject had prolonged kidney injury, requiring hemodialysis (HD) for 8 months, but still regained significant renal function. Our case is important to report in the literature because it adds perspective to the challenges of diagnosing HRS as well as determining eligibility for SLK in patients with cirrhosis and CKD.

Case report

A 56-year-old male with decompensated cirrhosis secondary to A1ATD type ZZ/30 presented with AKI. The patient's renal dysfunction was first noted on surveillance lab work, which revealed an elevated serum creatinine of 1.9 mg/dL (from a baseline of 1.0 mg/dL). His creatinine initially improved after discontinuation of diuretics and transition to large volume paracenteses (LVPs) for volume control. However, about 1 month later his serum creatinine rose to 3.4 mg/dL, prompting a hospital admission for expedited evaluation of his subacute kidney injury.

Despite having developed AKI in the setting of decompensated cirrhosis, the diagnosis of HRS as the etiology of his AKI was only transiently entertained. On admission, his urine electrolytes were consistent with pre-renal AKI and the renal function failed to improve after a trial of intravascular volume expansion challenge, both of which can be suggestive of HRS. Furthermore, he had no known recent exposure to nephrotoxins and no evidence of shock or hemodynamic compromise; renal ultrasound was unremarkable. However, his urinalysis was significant for 3+ proteinuria (spot urine protein:creatinine = 1400 mg/gCr), and urine microscopy revealed an active urine sediment, including dysmorphic red blood cells with both granular and red blood cells casts. This suggestion of intrinsic renal disease challenged the diagnosis of HRS, which is currently a diagnosis of exclusion.

A renal biopsy was performed, and the light microscopy slides showed diffuse acute tubular injury, mesangial proliferation, and focal interstitial infiltrate with lymphocytes. Immunofluorescence studies revealed 3+ IgA and C3 deposition in the mesangium and 1+ positivity for IgM in capillary loops. IgG was negative. Electron microscopy showed increased mesangial matrix deposits. Based on these biopsy findings, the patient was diagnosed with IgA nephropathy, for which he was treated with lisinopril, fish oil, and prednisone.

The patient's renal dysfunction progressed to end-stage renal failure in coming weeks and hemodialysis was initiated. He was subsequently listed for SLK on the advice of his clinicians. His model for end-stage liver disease (MELD) score was 34. After awaiting dual organ offers for several months, the patient decided to change his listing status to OLT alone. The motivation behind this was that his anticipated waiting time for an OLT alone would be much shorter than an SLK. Three days after unlisting himself for dual organ transplant, the patient underwent OLT.

Following OLT, the patient's average pre-hemodialysis serum creatinine improved from 7.1 mg/dL to 1.5 mg/dL. A measured CrCl was found to be 39 mL/min. Hemodialysis was subsequently discontinued. Two years post-OLT, his renal recovery has persisted. He has remained off of HD, and his creatinine has stabilized at 1.4–1.7 mg/dL (eGFR 40–50 mL/min). Given his degree of renal recovery following OLT, the patient was retrospectively diagnosed with HRS despite the presence of structural renal injury.

Discussion

Our case is noteworthy for a few reasons. First, it highlights the challenge of diagnosing HRS despite the existence of established diagnostic criteria, and it serves as a reminder to clinicians to consider this diagnosis in cirrhotic patients with renal dysfunction despite evidence of glomerular disease in the urine or on kidney biopsy. Second, it demonstrates the difficulty of deciding whether a cirrhotic patient with CKD should be eligible for an SLK, even in those with prolonged ESRD. Furthermore, it suggests that under the current OPTN/United Network for Organ Sharing (UNOS) medical eligibility criteria established for kidney allocation to SLK candidates, a significant proportion of patients are likely to receive a kidney graft that they do not need.

HRS is understood to be a functional injury to the kidneys involving maladaptive hemodynamic changes that include increases in nitric oxide-mediated splanchnic arterial dilatation and the compensatory upregulation of the renin–angiotensin–aldosterone system and sympathetic nervous system leading to renal vasoconstriction (10, 11). The current paradigm by which we diagnose HRS emphasizes it as a diagnosis of

exclusion. The International Ascites Club (IAC) HRS diagnostic criteria infer that the probability of a patient having HRS increases with the exclusion of shock, nephrotoxin exposure, and glomerular injury (based on the presence of significant proteinuria [>500 mg/24 hours] or hematuria [>50 RBC/hpf]). This is a challenging proposition because there is no pathophysiologic reason that HRS could not be present concurrently with ischemic/nephrotoxic acute tubular injury or glomerular injury. A more appropriate approach to emphasize may be to ponder whether HRS is the sole cause of kidney injury or whether it is superimposed on another etiology. Given that patients with cirrhosis are severely ill, they are undoubtedly at high risk of many types of renal insults. Low mean arterial pressures, gastric varices, and impaired coagulation function make ischemic injury common. Frequent exposure to infections, antibiotics, contrast dye, and proton pump inhibitors makes nephrotoxic injury common. In addition, it has been well documented since the 1940s that the majority of cirrhotic patients have biopsy-proven glomerular abnormalities, many of which contain IgA deposits, as was the case with our patient (12–23). Thus, the likelihood of having IgA deposits in a patient with cirrhosis and simultaneous HRS is not likely to be rare. The subject we report on had AKI and met five out of the six criteria for the diagnosis of HRS based on the 2015 ICA diagnostic guidelines. However, HRS was excluded as a diagnosis because his AKI was associated with the presence of an active urine sediment and a biopsy that confirmed IgA mesangial deposits. It was not until our patient had been on HD for 8 months and then had dramatic renal recovery immediately following OLT that the diagnosis of superimposed HRS was confirmed. This case therefore highlights the challenges associated with diagnosing HRS in patients with simultaneous glomerular disease.

Given the relative scarcity of organs available for transplant, it is imperative that cirrhotic patients with reversible kidney injury are accurately distinguished from those who have irreversible kidney injury in order to ensure just allocation of resources. Incorrectly diagnosing cirrhotic patients with irreversible renal failure leads to needlessly listing these patients for SLK. On an individual level, this translates to increased time on the transplant waitlist and its associated stress, anxiety, and relative negative quality of life (24–26). On a societal level, this means that fewer kidneys are available to ESRD patients, who face a 6% annual mortality on the kidney transplant waitlist (27).

Although our patient met eligibility for SLK based on the current criteria, his renal outcome was excellent after OLT alone. Therefore, this case underscores the challenges in rightly allocating kidneys for transplantation in patients with cirrhosis and kidney disease. Data show that those with mild CKD are not likely to benefit from SLK (7, 28). In terms of those with severe kidney disease or those requiring dialysis prior to transplant, data show a small survival benefit of about 5% at 1 year in those undergoing SLK versus OLT alone (29). However, the benefit of SLK may be especially difficult to determine in patients with HRS. Data from a single center showed that 33% of patients with HRS undergoing SLK had significant recovery of their native renal function post-transplant (30). Many of the kidneys being used for SLK have a low Kidney Donor Profile Index (KDPI) score (<35%). This has raised concerns among some members of the transplant community that organs with an expected long-term survival are preferentially being given to older recipients awaiting SLK over younger recipients awaiting an OLT alone (8, 9).

Conclusion

This case highlights the challenges associated with diagnosing HRS in patients with simultaneous glomerular disease. We feel it warrants a change in how we think about and discuss HRS. Clinical reasoning surrounding the diagnostic approach to HRS should be more inclusive of cases in which patients have HRS simultaneous to glomerular injury. Clinicians should be wary of excluding the diagnosis solely based on the presence of an active urine sediment. In addition, it should cause us to rethink if there is any role for performing a kidney biopsy in these patients. It is well appreciated that the bleeding and infection risk of performing a kidney biopsy is high in this population, but it should also be well appreciated that finding glomerular injury or other structural changes on biopsy will not by itself exclude HRS. This further re-enforces the fact that the risks associated with kidney biopsy in patients with cirrhosis far outweigh any potential benefits.

Furthermore, we hope that being familiar with cases such as ours, and similar ones reported in the literature (31), clinicians will more carefully consider for whom SLK is truly appropriate. The current medical eligibility criteria set the minimum duration during which kidney disease must be met for patients to be considered for SLK. It is critical that this should not be interpreted as a mandate that all patients who meet criteria undergo SLK as opposed to OLT alone. Our patient had excellent renal outcomes with OLT alone, despite meeting the criteria for SLT. We therefore argue that each case must be individually evaluated.

Conflict of interest

The authors declare no conflicts of interest with respect to research, authorship, and/or publication of this article.

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