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Atypical Presentation of Type 2 Hepatorenal Syndrome: Case Report and Literature Review

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Abstract

Hepatorenal syndrome is a reversible functional renal failure that occurs in patients with acute or chronic liver disease in the absence of underlying renal pathology. There have been identified two distinct types of hepatorenal syndrome namely, type-1 and type-2. Type-1 usually carries an abrupt evolution and a worse prognosis leading to death, if left untreated in less than 2 weeks; while type-2 carries a more subtle, chronic evolution and a better prognosis, leading to death in less than 4-6 months without treatment initiation. Clinical cases of type 2 HRS are rarely described in the literature and studies regarding this severe complication of liver cirrhosis are small population group trials.

In our case study, we describe the admission in the nephrology department of a 49-year-old male with moderate azotate retention and severe hyponatremia. He presented also with cryptogenic liver disease (model for end-stage liver disease MELD 35, Child-Turcotte-Pugh 12), refractory ascites and spontaneous bacterial peritonitis, along with severe chronic hyponatremia and moderate renal dysfunction. Because the patient upon admission met the major criteria for diagnosis of hepatorenal syndrome type 1, he was treated with repeated large volume paracentesis along with antibiotic therapy, in combination with plasma infusion and noradrenaline, achieving a slow but favorable evolution, with partial recovery of kidney function. In the following 9 months, serum creatinine remained relatively stable, between 1.38 and 1.55 mg/dL, making us place the positive diagnosis of Type-2 HRS. The patient is currently under multidisciplinary monitorization (gastroenterology and nephrology departments).

The particularities of this case were: relatively long evolution in a patient with type 2 hepatorenal syndrome, non-compliant to therapy, social case, impossible to include him on the waiting list for liver transplant due to chronic alcoholism. In conclusion, hepatorenal syndrome is mainly a diagnosis of exclusion, the process might be complex, intensive, and frequently prone to error.

Keywords: Hepatorenal syndrome; Acute kidney injury; Liver cirrhosis; Albumin; Hyponatremia; Liver transplantation

Abbreviations AKI: Acute Kidney Injury; ALAT: Alanine Aminotransferase; ASAT: Aspartate Aminotransferase; bid: "bis in die", twice a day; BP: Blood Pressure; Bpm: Beats Per Minute; BW: Body Weight; CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration; eGFR: Estimating Glomerular Filtration Rate; ER: Emergency Room; HCV: Hepatitis C Virus; HIV: Human Immunodeficiency Virus; HRS: Hepatorenal Syndrome; IAC: International Ascites Club; ICU: Intensive Care Unit; IgA: Immunoglobulin A; IV: Intravenous; MELD: Model For End-Stage Liver Disease; MRI: Magnetic Resonance Imaging; OLT: Orthotopic Liver Transplant; s.c.: subcutaneous; SBP: Spontaneous Bacterial Peritonitis; TLVP: Therapeutic Large-Volume Paracentesis; WBC: White Blood Cells

Introduction

Kidney failure is common in advanced chronic liver disease, especially in patients with ascites, usually due to one or more events that further compromise renal perfusion. However, we must consider that there are several factors which decrease the diagnostic accuracy of serum creatinine in cirrhotic patients; particularly muscle wasting that characterizes such patients [1].

Hepatorenal syndrome (HRS) is not the most diagnosed form of acute kidney injury (AKI) in patients with liver disease, it really accounts for less than 10% of all cases in current clinical practice, other causes, like volume unresponsive AKI and acute tubular necrosis being much more common. HRS is characterized by functional impairment of renal function due to vasoconstriction of the renal arteries, associated with a preserved tubular function on a nearly normal renal histology. It may occur both spontaneously, due to well-known triggers such as spontaneous bacterial peritonitis (SBP), as well in the absence of precipitating factors [2].

In 1996, the International Ascites Club (IAC) published the diagnostic criteria for HRS, later revised and updated (2007). The revised IAC criteria include: "(i) cirrhosis with ascites, (ii) serum creatinine level >1.5 mg/dL, with removal of creatinine clearance, (iii) no improvement in serum creatinine after ≥ 2 days with diuretic withdrawal and volume expansion with albumin, rather than saline for plasma expansion, (iv) absence of shock or recent use of nephrotoxic drugs, (v) absence of parenchymal kidney disease, indicated by proteinuria >500 mg/day, microscopic hematuria (>50 red blood cells

per high power field), and/or abnormal renal ultrasonography, and last, but not least, removal of the previous minor diagnostic criteria (urine volume, urinary and serum sodium)" [3].

According to evolution and presence of precipitating factors, there are described two types of HRS: Type-1 HRS is characterized by an acute deterioration in renal function and is considered a form of pre-renal AKI which is commonly precipitated by a bacterial infection (SBP being the most common cause), and Type-2 HRS which is considered a more chronic form of renal dysfunction and is very commonly associated with a diuretic-resistant ascites [4].

The clinical expression of HRS is one of a pre-renal failure which is not responding to volume expansion. HRS must be considered a diagnosis of exclusion of other causes of AKI in cirrhotic patients. The latest data confirm that HRS carries the worst prognosis of all complications of liver cirrhosis, carrying the highest mortality rate (more than 50% of such patients die in an interval of several months). Treatment of HRS involves the use of vasoconstrictors and volume expansion with albumin, their effectiveness is, however, low (40-50% of cases) and recurrences are frequent. Consequently, orthotopic liver transplant (OLT) is currently considered the single long-term therapeutic approach but is restricted by the high mortality rate and the lack of available grafts [5,6].

Case Presentation

A 49-year-old male, with a history of liver cirrhosis, diagnosed seven years before, due to hepatitis C virus infection and alcohol abuse, and without renal diseases in personal antecedents, had repeated admissions for decompensation of liver cirrhosis during the past 2 years. Currently, he presented to the ER complaining of lumbar pain, oligo-anuria, important abdominal distention, followed by progressive worsening dyspnea. Physical examination revealed: good mental status, fetor hepaticus, pale skin with scleral jaundice, palmar erythema, discreet white pitting pretibial edema, caput medusae and important ascites with periumbilical hernia. His blood pressure was 105/60 mmHg, with regular heart rate of 84 Bpm and normal cardiac auscultation. The abdominal palpation revealed: an enlarged, tensed abdomen with diffuse pain on palpation, painless hepatomegaly, splenomegaly grade II and negative Giordano maneuver.

Paraclinical findings: Hemoglobin= 8.6 g/dL, Hematocrit=22%, WBC=3300/mmc, Platelets=35.000/mmc, Urea=156 mg/dL, Creatinine=2.85 mg/dL, Serum glucose=86 mg/dL , Total Bilirubin=4.5 U/L / Direct Bilirubin=2.8 U/L, Alkaline Phosphatase=198 U/L, GGT=78 U/L, ALAT=115 U/L; ASAT=250 U/L, Serum Na=119 mmol/L, Urinary Na$^+$=12 mEq/L/day, K$^+$=2.9 mmol/L, Bicarbonates=15 mmol/L, Total serum protein=5 g/L, Serum albumin=1.8 g/L, fibrinogen=110 mg/dL, serum amylase=18 U/L, anti HCV antibodies positive, cryoglobulines negative, viral markers for hepatitis B and HIV-test were negative

Urinalysis with urinary sediment had normal aspect.

Abdominal ultrasound examination was challenging due to abundant abdominal subcutaneous tissue and important ascites: Diffusely non-homogenous hyper-echogenic liver, with regenerative nodules; Right lobe=163 mm, Left lobe=72 mm, Caudal lobe=44 mm, Portal vein=15 mm, Splenic vein=10 mm, Gallbladder=6 mm (wall thickness, with double contour); pancreas: irregular, hyper-echogenic; spleen: increased dimensions (138/80 mm); both kidneys with normal longitudinal axis ~ 118/68 mm, cortical diameter 19 mm, no

hydronephrosis; peritoneal cavity: important ascites. Because of the basic limitation of ultrasound exam due to patient's obesity and ascites, with poor visibility of the bile ducts and the posterior segments of the liver, associated with increased serum creatinine levels, we preferred MRI imaging for imagistic evaluation with better sensitivity and specificity (Figure 1).
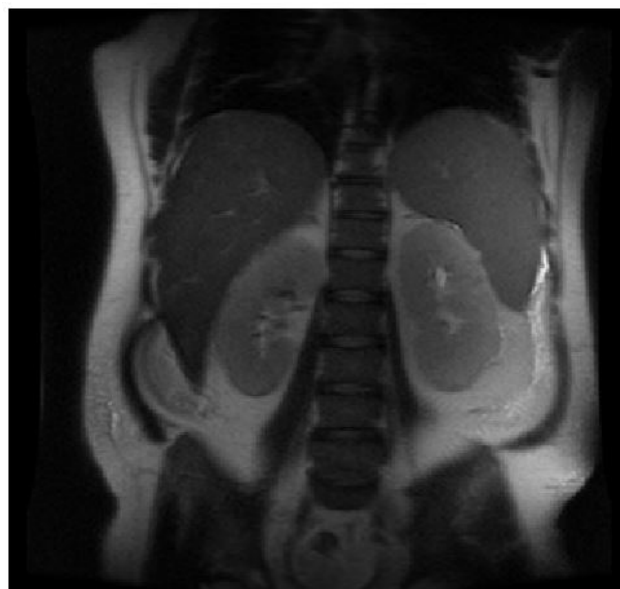
Figure 1: Abdomino-pelvic MRI: Liver and spleen with enlarged diameters, enlarged portal vein along with obvious ascitic fluid collection and radiographically normal kidneys.

Taking into consideration the medical history, along with the clinical and paraclinical findings, the following manifestations were noted: important ascites, hepato-splenomegaly, icteric sclera, anuria, hepatic cytolysis, cholestasis syndrome, and moderate azotate retention. These findings increased our suspicion for either Hepatorenal syndrome/AKI associated with Alcoholic liver disease and HCV infection vs. other conditions which combine liver and kidney damage.

Because of the suspicion of hepatorenal syndrome, we started the treatment with Ringer solution 500-1000 mL/day (to correct hypokalemia and hyponatremia), according to diuresis, followed by 50 mL of Sodium Bicarbonate 8, 4% IV (to correct metabolic acidosis), fresh frozen plasma and albumin administration. Due to the development of persistent arterial hypotension, we were forced to administer dobutamine 5-10 mcg/kg/min IV, gradually increasing to 12 mcg/kg/min IV, without achieving recovery of diuresis (only 0.5-0.7 L/day), demanding his transfer to the Intensive care unit (ICU).

In the ICU, diagnostic peritoneal puncture was performed and spontaneous bacterial peritonitis (SBP) was diagnosed (leukocytes in the ascites fluid >500/ml, with >50% neutrophils), thus performing repeated large volume paracentesis along with antibiotic therapy (Cefuroxime 1 g bid IV, 7 days) was indicated. Even though the role of therapeutic large-volume paracentesis (TLVP) in hepatorenal syndrome is controversial, accepting the presence of tense ascites, in our patient was undoubtedly beneficial.

In addition, Noradrenaline IV 2-3 mg/hour was administrated, in order to raise the systolic BP over 110 mmHg, and albumin replacement was given for 3 days as IV bolus (1 g/kg BW per day, total dose 100 g). The serum creatinine failed around the value of 1.46 mg/dL, with an eGFR CKD-EPI of 42 mL/min/1.73 m². The hospitalization was prolonged for 1 month, because of the oscillating pattern of evolution. It is also worth mentioning that the patient's MELD score on admission was 35, translating to a 52.6% 3-month survival rate.

The patient did not need renal replacement therapy and he was released from the hospital in a relatively good condition. In the next months, he was re-admitted repetitively, every 1-2 months, for refractory ascites, with relatively stable evolution after repeated paracentesis, albumin or fresh frozen plasma administration and a combination of anti-aldosteronic drug (spironolactone) with loop-diuretic (furosemide) administered cautiously, due to the high risk of encephalopathy and dyselectrolytemia. Serum creatinine remained relatively stable during the 9 month period, between 1.38 and 1.55 mg/dl, and he is currently under multidisciplinary monitorization (gastro-enterology and nephrology departments). In this context, our final diagnosis was: Hepatorenal syndrome type 2. Mixed etiology liver cirrhosis (Viral C+ ethanolic) class Child-Pugh B. Pancytopenia-hematologic hypersplenism.

The particularities of this case were: relative long evolution in a patient with type 2 HRS, non-compliant to therapy, social case, as well as the impossibility to include the patient on the waiting list for liver transplant, because he could not give up alcohol consumption.

Discussion

The patients who have liver disease may also have kidney disease associated with their liver disease and not HRS. "Almost any liver disease has a specific but usually rare renal disease glomerulonephritis, IgA nephropathy (frequently associated in ethanolic patients) or renal distal tubular acidosis etc. So, it is important to exclude these diseases first. The exclusion is done usually clinically, in the absence of proteinuria and in the absence of cells and casts in the urine" [7].

It is recognized that "sepsis is one of the most known intrinsic factors of HRS and circulatory dysfunction is usually the key of evolution in cirrhotic patients, that is why pharmacological intervention is needed to improve cardiac function of these patients" [6,7].

Type 2 HRS is a functional impairment of kidney function that occurs in patients with advanced cirrhosis and is usually characterized by the association of refractory ascites with poor response to diuretics. From the perspective of kidney function, in type 2 HRS, the impairment of kidney function remains relatively stable, usually for a longer period of time. Type 2 HRS is an uncommon cause of kidney failure in patients with cirrhosis, in this manner it is challenging to realize large-group studies. In a recent study, concerning hospitalized patients with cirrhosis and kidney failure, only 5% of patients had type 2 HRS which represented an incidence of 3.5 patients/year [7].

In the past, dobutamine and dopamine were the most used drugs to be given for HRS, but due to the lack of significant positive results, they are not recommended anymore. The main treatment follows the control of underlying conditions with improvement of liver function, but also therapeutic measures which are meant to reverse the AKI associated with HRS are needed. In case of continuous monitoring, the

recommendations are: "treatment with an intravenous infusion of norepinephrine at 0.5-3 mg/hour to raise the mean arterial BP over 100 mmHg, and the administration of albumin IV bolus for at least two days (1 g/kg per day, up to 100 g). Vasopressin at 0.01 units/min titrated may be an alternative, or better terlipressin, as an intravenous bolus (1 to 2 mg every 4-6 hours) in association with albumin or a combination of octreotide (s.c. 100-200 mcg three times daily or continuous intravenous infusion at 50 mcg/hour) with midodrine (starting at 7.5 mg three times a day, max. 45 mg daily), and iv albumin)" [8].

Octreotide is a somatostatin analogue that induces local vasoconstriction on vascular smooth muscle of the superior mesenteric arterial bed, its effect occurring only in the presence of vasoconstrictors, activators of the protein kinase C. Midodrine is an alpha-adrenergic receptor agonist and the drug most commonly used in the treatment of HRS in the United States, and is the regimen we used with success in our patients with low BP. The combination of octreotide and midodrine has been shown to exert a positive effect on renal function of HRS patients, with complete reversal in variable percentages (30-49%). Midodrine is administered orally with a starting dose of 5-10 mg three times/day up to a maximum dose of 12.5 mg three times/day and octreotide subcutaneously at an initial dose of 100 μg three times/day up to a maximum dose of 200 μg three times/day) [9,10].

In contrast with the substantial information regarding type 1 HRS, there are few literature data about the pharmacological treatment in patients with type 2, in spite of the fact that therapy is generally well tolerated and usually reverses type 2 HRS, but with an increase rate of relapses after treatment withdrawal. In the meantime, there is no information about the efficacy of therapy on the evolution of patients with type 2 HRS. Due to this lack of information, the existing international guidelines do not recommend the use of vasoconstrictors and albumin in the therapy of type 2 HRS, except for those waiting for liver transplant [11]. In this situation, appropriate therapy of type 2 HRS, with partial reversal of the syndrome, and sometimes dialysis, when indicated, could improve the prognosis of patients while on the waiting list for transplant, in comparison with nontreated patients. Moreover, the "improvement of renal dysfunction at the time of transplantation would have a beneficial effect on the outcome after transplantation in general, and on kidney function, in particular" [12].

Conclusion

Hepatorenal syndrome (HRS) is a relatively rare, but severe kidney dysfunction that occurs in liver cirrhosis and is a frequent cause of death among these patients. It is mainly a diagnosis of exclusion; the process might be complex, intensive, and frequently prone to errors. That is why, in order to gain time for our patient's benefit, in some patients that do not fulfill completely the IAC diagnostic criteria, we start treatment as having "*presumed*" HRS, based on the index of clinical suspicion.

In type 2 HRS we have demonstrated that the progression of kidney failure is slow, with a less-marked reduction in GFR and a better prognosis, especially if the patient encounters the criteria for liver transplantation.

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