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Hepatitis B Reactivation in HBsAg Negative Renal Transplant Patients with Evidence of Previous HBV Infection: A Not Neglectable Occurrence

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Abstract

Hepatitis B virus (HBV) infection is frequent among patients with chronic kidney disease (CKD). HBV reactivation after kidney transplant (KT) is more common in patients with HBsAg+; however, it can also occur in previously infected individuals, particularly those with HBsAg negative and total antiHBc positive (HBsAg-/antiHBcT+). However, reactivation in this population has scarce and conflicting data. This study aimed to assess the reactivation risk in KT recipients with previous HBV infection (antiHBcT+). A retrospective cohort study was conducted, including patients with KT between January 1993 and December 2012 with HBsAg+ (G1) and with previous HBV infection (antiHBcT+) (G2). A total of 10,493 transplants were performed in this period. A total of 203 patients were included (122 HBsAg+ and 81 HBsAg-/anti-HBcT+). The reactivation of infection occurred in 24.6% (30/38) patients and 9.8%

(8/30) in G1 and G2, respectively. Detectable HCV RNA, indicating HCV coinfection, was the only variable related to reactivation in patients with antiHBcT+, protecting its occurrence (p: 0.001). In conclusion, reactivation of HBV infection in KT recipients with the previous infection, occurring in approximately 10% of cases, should be considered. Complete HBV serology is recommended before KT, and patients with HBsAg-/anti-HBcT+ should be monitored after the procedure. Prophylaxis may be indicated when adequate follow-up is not feasible. HCV coinfection appears to be a protective factor for reactivation.

Keywords
Kidney transplant (KT); hepatitis B virus (HBV); reactivation

1. Introduction

Reactivation of hepatitis B virus (HBV) infection is commonly observed in patients with immunosuppression. However, the diagnosis of reactivation is often challenging and is associated with an elevated risk of decompensation and hepatic failure [1-4]. However, HBV reactivation is heterogeneous; thus, the outcome associated with its occurrence is variable in the literature.

Reactivation is characterized by the virus escaping the immune control, leading to an increase in viral replication, followed by various degrees of liver damage. This occurrence is observed with higher frequency in patients with HBsAg+ and those who are previously infected (HBsAg- and total antiHBc+, with or without antiHBs). The condition is characterized by a rapid increase in aminotransferases, followed by hepatic decompensation and death [3-6].

Reactivation of HBV infection can be caused by chemotherapy, autoimmune diseases under immunosuppression, HIV infection, use of immunomodulating drugs, and in patients who underwent transplantation [7, 8]. Regarding solid organ transplantation, HBV reactivation is more common in kidney transplants (KT), especially in patients with HBsAg+ [9]. Reactivation in previously HBV-infected patients has been reported in the literature; however, there is no consensus regarding the frequency and, consequently, the indication of antiviral prophylaxis in this special group of patients [10-14].

This study aimed to determine the risk and factors associated with reactivation in HBsAg-negative KT patients with evidence of previous HBV infection (antiHBcT+).

2. Patients and Methods

This is a retrospective study of patients who underwent transplantation between 1993 and 2012, followed at the Hospital Sao Paulo and Hospital do Rim e Hipertensao, Sao Paulo, Brazil. The patients with HBsAg+ (G1) and HBsAg- with antiHBcT+ (G2) KT were included in the study. The inclusion criteria were patients above 18 years of age and with more than 5 years of transplant. Patients with alcohol consumption higher than 20 g/day and those with isolated anti-HBs were excluded.

2.1 Laboratory Tests

The electrochemiluminescence immunoassay (*Cobas e601 Immunology analyzer, Roche Diagnostics, Basel, Switzerland*) was used to assess serological markers HBsAg, antiHBcT, HBeAg, antiHBe, and antiHBs. Anti-HCV antibodies were detected using an immunoassay *(Elecsys® Anti-HCV II Roche Diagnostics, Basel, Switzerland)*. HBV and HCV viral load were analyzed using quantitative Polymerase Chain Reaction in Real-Time (PCR-RT), HBV DNA (*Abbott Real-Time HBV, Abbott Park, Illinois, USA*), and quantitative PCR-RT HCV RNA (*Abbott Real-Time HCV, Abbott Park, Illinois, USA*) in the serum samples.

The reactivation of HBV infection was defined as HBsAg seroconversion in HBsAg-/antiHBcT+ and/or elevation of HBV viral load >1 log/mL and an increase of ALT (alanine aminotransferase) >5× ULN (upper limit of normality) and/or >3× baseline values [3].

2.2 Variables Analyzed

The following variables were analyzed: age (years), sex, time of transplantation (years), type of donor (alive or deceased), etiology of renal disease, time on dialysis (months), and type of immunosuppression. HCV coinfection was defined by the presence of HCV RNA. Patients were also evaluated regarding the presence of cirrhosis (by clinical, laboratory, image, or histopathological analysis). HBV reactivation, decompensation, graft loss, hepatocellular carcinoma, liver transplantation, and death were the evaluated outcomes.

2.3 Statistical Analysis

The exploratory data analysis included mean, standard deviation, and median for continuous variables, and frequency and proportions to categorical variables. The asymmetry, kurtosis, and Kolmogorov-Smirnov tests were used to analyze the normality distribution of continuous variables. Comparison between groups was analyzed using Student's t-test or Mann-Whitney test for continuous variables and Qui-square or Fischer test for categorical variables. To evaluate the simultaneous effect of variables to predict reactivation, a multivariate model was applied. Statistical tests were performed using IBM-SPSS Statistics software version 24 (IBM Corporation, NY, USA). $P< 0.05$ was considered statistically significant.

The study was approved by the Ethical Committee from the Federal University of Sao Paulo (0396/2017).

3. Results

Between January 1993 and December 2012, 10,439 patients underwent KT at our institution. Two hundred and three patients were retrospectively included in the study (122 HBsAg+ and 81 HBsAg-/antiHBcT+). The mean time of follow-up was 11.3 ±5.6 years. The general characteristics of the patients are described in Table 1.

Table 1 General characteristics of 203 patients who underwent the renal transplant in the study.

Characteristic	n (%)
Age, years	40.2 ±11.2
Sex, n (%)	
Male	135 (66)
Female	68 (33)
CKD* etiology	
Systemic arterial hypertension (SAH)	37 (18.2)
Diabetes mellitus (DM)	8 (3.9)
Glomerulopathy	43 (21.2)
Polycystic disease	5 (2.5)
Undetermined	82 (40.4)
Other causes	28 (13.8)
Time of dialysis, months	70.5 ±47.4
Time of transplantation, years	10.0 (5–33)
Donor, n (%)	
Deceased	116 (57.7)
Living	85 (42.3)
HBV profile before KT, n (%)	
HBsAg+	122 (60.1)
HBeAg+	61/122 (50.0)
HBsAg-/antiHBc total +	81 (39.9)
Cirrhosis, n (%)	19 (9.3)
HCV coinfection	
PCR RT HCV RNA, n (%)	70 (34.4)
Immunosuppressors	
Including azathioprine, n (%)	96 (47.3)
Including cyclosporine, n (%)	130 (64.0)
Including mycophenolate, n (%)	71 (35.0)
Including tacrolimus, n (%)	52 (25.6)
Antiviral HBV therapy before reactivation, n (%)	68 (33.5)

* **CKD**- chronic kidney disease; **KT** - Kidney transplant; **HBV**- Hepatitis B virus; **HCV** - Hepatitis C virus; **HBsAg** - Hepatitis B surface antigen; **HBeAg** - Hepatitis B virus E antigen; **anti-HBcT** - Total antibody against the core HBV antigen

All patients were on triple immunosuppression therapy, including prednisone. Cyclosporine was included in the immunosuppression scheme in 64% of patients, azathioprine in 47%, mycophenolate in 35%, and tacrolimus in 26%.

The patients with HBsAg+ were compared to those with HBsAg-/antiHBcT+ and the results can be observed in Table 2.

Table 2 Comparative analysis between patients with HBsAg+ *vs* HBsAg-/anti-HBcT+.

Characteristics	HBsAg+ (n = 122)	anti-HBcT+ (n = 81)	P-value
Age (years), mean	39.9 ±11.4	40.6 ±10.9	0.707
Sex, n (%)			
Male	87 (71.3)	48 (59.3)	0.075
Female	35 (28.7)	33 (40.7)	
Donor, n (%)			
Deceased	67 (55.8)	49 (60.5)	0.512
Alive	53 (44.2)	32 (39.5)	
Cirrhosis, n (%)			
	13 (10.7)	6 (7.4)	0.426
HCV RNA positive, n (%)			
	22 (1.3)	48 (59.0)	**<0.001**
Treatment pre-KT/pre-reactivation			
	68 (55.7)	0 (0)	**<0.001**

KT: kidney transplant

Hepatitis B reactivation was observed in 30/122 (24.6%) of patients with HBsAg+ and in 8/81 (9.8%) of those with HBsAg-/antiHBcT+ (P: 0.008). The median time to reactivation was 56.7 months after transplantation (3 to 278 months). During reactivation, eight (21.1%) patients died, five (13%) lost renal graft, and four (10.5%) presented hepatic decompensation. The immunosuppression scheme was stable at the time of reactivation, and no patients were on high doses of prednisone or receiving anti-thymocyte globulin. None of these patients was receiving antiviral treatment before reactivation.

HBsAg-/antiHBcT+ with reactivation of HBV infection (n = 8) was compared to HBsAg-/antiHBcT+ without reactivation to identify variables associated with this occurrence. Younger age, the presence of cirrhosis, and the absence of HCV coinfection were associated with the risk of reactivation (Table 3). After the logistics regression analysis, the only variable associated with reactivation was HCV coinfection (P: 0.001), which seems to be a protective factor (Table 4).

Table 3 Comparison between HBsAg-/anti-HBcT+ with and without reactivation.

	With reactivation n = 8	No reactivation n = 73	P-value
Sex, n (%)			
Male	6 (12.5)	42 (87.5)	0.289
Female	2 (6.1)	31 (93.9)	
Age (years), mean	32.88 ±9,55	41.4 ±10.75	**0.035**
Cirrhosis, n (%)			
	2 (33.3)	4 (66.7)	**0.045**

HCV RNA, n (%)			
Detected	1 (2.1)	47 (97.9)	**0.002**
Mycophenolate n (%)	1 (4.8)	20 (95.2)	0.332
Tacrolimus n (%)	0 (0)	10 (100)	0.331
Azathioprine n (%)	6 (11.5)	46 (88.5)	0.401
Cyclosporine n (%)	7 (11.3)	55 (88.7)	0.396

Table 4 COX multivariate regression model for reactivation outcome among anti-HBcT+ patients (n: 81).

	Initial model		**Final model**	
	Hazard ratio (IC 95%)	**P**	**Hazard ratio (IC 95%)**	**P**
Age	1.020 (0.980–1.061)	0.337		
Sex	1.276 (0.556–2.927)	0.565		
Donor	1.781 (0.779–4.072)	0.171		
HCV RNA	0.088 (0.019–0.407)	0.002	**0.084**	**0.001**
Cirrhosis	1.347 (0.389–4.664)	0.638		

4. Discussion

Hepatitis B and C are important causes of morbimortality in patients who undergo renal transplants. Despite the decreasing prevalence of HBV infection in patients with CKD, the liver disease associated with this virus remains a challenge [15, 16].

Studies regarding HBV infection in patients with KT have been published since the 1980s [17], and the risk of reactivation is high in patients with HBsAg. These patients should undergo HBV antiviral therapy before transplantation to avoid reactivation. However, in HBsAg-negative patients with evidence of previous HBV infection, the risk of reactivation is not established, and the use of antiviral therapy is controversial [8, 11, 18].

In the present study, patients with previous contact with HBV (HBsAg-/anti-HBcT+) were compared to those with HBsAg+ regarding the incidence of reactivation. Moreover, the factors associated with this event were evaluated in the group of patients with previous infections. During the follow-up period, 38 patients presented reactivation of HBV infection: 24.6% (30/122) in HBsAg+ group *vs.* 9.8% (8/81) in HBsAg-/antiHBcT+ group patients. Among the 38 patients that presented reactivation, eight (21.05%) had acute hepatic insufficiency and were evaluated to death since they were not receiving prophylaxis of reactivation at that time, five (13%) lost the renal graft, and four (10.5%) presented hepatic decompensation.

HBV reactivation in HBsAg-negative patients was first published by Degos et al. in 1988, demonstrating that 7/35 HBsAg-negative patients presented evidence of viral replication after KT induced by immunosuppression [19]. Another study evaluated a retrospective cohort of 93 KT patients with evidence of previous HBV infection between 1995 and 2007. Si patients (6.5%) were identified with HBV reactivation [14]. A similar immunosuppression regimen was observed in patients with and without reactivation, similar to the present study. The study also demonstrated that antiHBs levels higher than 100 UI/mL should be maintained to prevent reactivation. In our study, 2/8 patients with reactivation (25%) had detectable anti-HBs, while 47/73 (64%) patients without

reactivation were anti-HBs positive. There was no difference among the groups, probably owing to small numbers (p = 0.473); however, the results suggest that antiHBs may be responsible, to some extent, for minimizing the risk of reactivation.

In our study of KT patients with previous HBV infections, the presence of positive HCV RNA was the only variable independently associated with reactivation. Hepatitis C active viremia appeared to have protected patients from reactivation, probably owing to the viral interference phenomena. Recently it was demonstrated that HCV infection could inhibit HBV replication in cell models by suppressing HBV core and S promoter II activities [20].

In the present study, none of the patients with HBsAg-/antiHBcT+ were receiving antiviral treatment before transplantation. The approach to patients with antiHBcT+ who underwent KT is controversial. According to the *European Association for the Study of the Liver – EASL* – 2017, patients with HBsAg-/antiHBcT+ KT should not undergo prophylaxis to reactivation; however, monitoring of HBsAg is indicated to identify HBsAg seroconversion. In this scenario, antiviral therapy is indicated independent of alanine transaminase (ALT) levels [21]. Indian guidelines for the management of HBV infection for patients receiving immunobiological, chemotherapy, or immunosuppression recommend HBV-DNA determination each 3/3 months in the first year and annually thereafter for all patients undergoing solid organ transplantation [22]. The guidelines of the *American Association of Liver Diseases – AASLD* – 2018 [18] state that the risk of reactivation in patients with previous HBV infection is low. However, depending on the intensity of immunosuppression, antiviral therapy prophylaxis for a short period (6 to 12 months), when the immunosuppression is more intense, is recommended. After antiviral therapy discontinuation ALT should be monitored every 3 months.

This study has some limitations. The number of patients with previous HBV infection was smaller than patients with HBsAg+ since complete pre-transplant HBV serology was not routine at our institution at the time of the study. However, the number of reactivations in the previously infected patients cannot be negatable even with this small sample. Therefore, another limitation was the comparison between antiHBcT+ patients with and without anti-HBs since complete HBV serology was not routinely performed. However, immunosuppressed antiHBcT+ patients should be treated using the same approach independent of the presence of anti-HBs [8].

All these limitations are inherent to a retrospective study; however, in any case, many important data and observations could be obtained in a large series of HBV-infected patients in KT recipients, whose data are scarce in the literature.

In summary, the indications of antiviral prophylaxis for all patients with HBsAg+ before renal transplantation are well-established. However, the risk of reactivation in patients with the previous infection should not be neglected. The initiation of pre-transplant antiviral therapy in this group of patients is controversial, being more reasonable to monitor ALT for 3/3 months, followed by HBV DNA, in case of elevation of ALT.

Complete HBV serology should be recommended for all pre-KT patients, aiming to avoid complications depending on the HBV profile. According to the results, the patients can undergo laboratory monitoring of ALT and HBV DNA, pre and post-KT, initiation of antiviral therapy if indicated, and HBV vaccination for susceptible patients and those with previous infection and low or undetectable levels of anti-HBs.

In conclusion, this study involving a large cohort of patients who underwent renal transplants demonstrated that HBV reactivation in patients with previous HBV infection was less frequent than

in patients with HBsAg; however, not neglectable, occurring in approximately 10% of patients. The results suggest that patients with previous HBV infection should be closely monitored after renal transplantation for early detection of reactivation and initiation of antiviral therapy. Prophylaxis may be indicated when adequate follow-up is not possible. Moreover, HCV infection appears to protect against HBV reactivation, probably owing to viral interference.

Author Contributions

Ana Paula Leopercio: Project development, data collection, wrote the paper; Christini Emori: evaluation of patients, data collection; Elisabete Calore Neiva: data collection; Ana Lucia Silva Souza, evaluation of patients, data collection; Ana Cristina Amaral: project development, corrected the text, Gustavo Almeida Vieira: evaluation of patients, data collection; Raimundo Araujo Gama: data collection; Jose Osmar Medina-Pestana: project development, data analysis, text correction; Maria Lucia Ferraz: project development, data analysis, edition of final version.

Competing Interests

The authors have declared that no competing interests exist.

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