Hepatitis B reactivation after COVID-19: just a coincidence or a causal relationship?

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ABSTRACT

A 48 year-old man was evaluated because of a sudden raise in his liver function tests. He had a prior history of an acute hepatitis B infection, which spontaneously resolved in 2015 and a recent COVID-19 infection. As he only developed a mild disease, he did not receive steroids or convalescent plasma, or any other drugs. Seven weeks after having acquired the infection, he presented an acute hepatitis. Every known etiological factor was discarded. New serological status for hepatitis B was evaluated, and we discovered a sero-reversion. This situation could often be seen after immunosuppressive treatments, but our patient receive none of them. We started Entecavir and a rapid negativization of his viral load was observed as well as a normalization of his liver tests. If this reactivation was a consequence of COVID-19 or not is still not clear for us, but we believe that this case could raise awareness among physicians.

KEYWORDS

Hepatitis B; Hepatitis B reactivation; COVID-19.

INTRODUCTION

Coronavirus disease 2019 (COVID-19), the illness caused by SARS-CoV-2 was declared pandemic in March 2020 [(1)] and its first case in Argentina was in that month. It has been reported that this novel zoonotic virus enters into target cells by binding to the angiotensin-converting enzyme 2 (ACE2) [(2)] which acts as a viral receptor.
ACE2 is present in billiary and liver epithelial cells, so the liver is a potential target for this viral infection. Abnormal levels of aminotransferases are reported in 14-58% of infected patients. [(3)]
This may reflect a direct viral cytopathic effect and/or immune damage secondary to the inflammatory response to the virus. [(4)]
Cirrhotic patients are at higher risk of death from COVID-19, and probably people living with chronic liver diseases (CLD) carry a higher risk also. The impact on Non Alcoholic Fatty Liver Disease is controversial but, metabolic syndrome (which is a risk factor for fatty liver disease) is very well associated with COVID-19 severity. [(3)]
Recently a paper from the United Arab Emirates reported a case of an hepatitis B virus (HBV) reactivation (HBVr) in a patient with COVID-19 infection. [(5)]
Here we report a case of HBV sero-reversion after COVID-19 infection. To the best of our knowledge, this is the first case reported in Latin America.

CASE REPORT

A 48 year-old man was referred to hepatology medical consultation because of an acute hepatitis (TABLE 1). Physical examination was normal. His medical history revealed an acute HBV infection in 2015 which resolved after 8 months (positive Antibodies to Surface Antigen –AntiHBs- and negativization of HBV Surface Antigen –HBsAg-). Another key point was that seven weeks before this acute hepatitis, he had been admitted as an inpatient because of mild COVID 19 infection. Neither pneumonia nor other complications were present. He did not receive steroids, plasma, antibiotics or any off label drug against SARS-CoV2. He was discharged after 6 days. Liver function tests (LFTs) during his hospitalization were normal. At the moment of his hepatology evaluation, nasal swabs for COVID-19 were negative. Abdominal doppler ultrasound was normal. We ruled out hepatitis A, C and E (viral load for hepatitis C and PCR in blood and stools for hepatitis E were negative) and acute Cytomegalovirus and Epstein Barr infection. Auto-antibodies for autoimmune hepatitis were negative. Gammaglobulins and Ceruloplasmin were within normal values. No alcohol consumption, toxics, herbal medicines or traditional ones were referred. A re-assessment on HBV status was done: HBsAg, HBV core and antibodies against hepatitis B e antigen (Anti HBe) were positive; while Anti HBs and Antigen e (HBeAg) tested negative. HBV viral load was 9,450 UI/ml. HIV and hepatitis D (HDV) were ruled out. Protrombin was within normal values. An HBV seroreversion (HBVr) was diagnosed. Entecavir was started, LFTs returned to normal values and DNA became negative.

TABLE 1: Laboratory Data (2015: Acute Hepatitis B and 2020: Hepatitis B reactivation)

YEAR 2015	**TB** (mg/dl) (normal)	**AST** (UI/ml) (normal)	**ALT** (UI/ml) (normal)	**PT** (%)	**HAV** IgM/ IgG	**HBV**					**HCV Ab/VL** (UI/ml)
						HBs Ag	**HBVcore IgM/IgG**	**HBeAg**	**Anti HBe**	**Anti HBs**	
Week 1	2.5 (1)	312 (40)	276 (42)	100	NA	NA	NA / NA	NA	NA	NA	NA
Week 3	2.8 (1)	676 (40)	548 (42)	100	**(-)/(+)**	**(+)**	**(+)/(+)**	NA	NA	NA	**(-)** / NA
Week 4	3.7 (1)	1863 (40)	1581 (42)	96	NA	NA	NA	**(+)**	(-)	NA	NA/ <15
Week 6	2.4 (1)	2070 (40)	1861 (42)	98	NA	NA	NA	NA	NA	NA	NA
Month 2	1 (1)	1543 (40)	1489 (42)	NA	NA	NA	NA	NA	NA	NA	NA
Month 4	1 (1)	36 (40)	87 (42)	NA	NA	(+)	NA	**(-)**	**(+)**	NA	NA
Month 6	1 (1)	31 (40)	26 (42)	NA	NA	(-)	NA	NA	NA	NA	NA
Month 8	1 (1)	35 (40)	37 (42)	NA	NA	(-)	NA	NA	NA	(+)	NA
YEAR 2020											
Week 1	1.9 (1)	807 (32)	832 (32)	NA	NA	NA	NA	NA	NA	NA	NA
Week 3	2.4 (1)	932 (32)	857 (32)	99	(-) /(+)	NA	NA	NA	NA	NA	(-)/NA
Week 4	2.9 (1)	803 (32)	819 (32)	95	NA	(+)	(+)/(+)	(-)	(+)	(-)	(-) /<15
Week 6	2.1 (1)	545 (32)	723 (32)	97	NA	NA	NA	NA	NA	NA	NA
Week 7	2.1 (1)	379 (32)	590 (32)	99	NA	NA	NA	NA	NA	NA	NA
Week 8	1.7 (1)	241 (32)	370 (32)	99	NA	NA	NA	NA	NA	NA	NA
Week 10 HBV VL: 9,450 UI/ml (received in week 9) **ENTECAVIR 0.5mg/day** (started in week 10)											
Week 12	1.5 (1)	96 (32)	126 (32)	NA	NA	NA	NA	NA	NA	NA	NA
Week 16	1.1 (1)	90 (32)	119 (32)	NA	NA	(+)	(-)/(+)	(-)	(+)	(-)	NA
Week 20	0.7 (1)	43 (32)	81 (32)	NA	NA	NA	NA	NA	NA	NA	NA
Week 24	0.9 (1)	27 (32)	25 (32)	NA	NA	(+)	(+)	(-)	(+)	NA	NA
4 months and a half since ENTECAVIR was started: HBV VL < 20 UI/ml											
Week 28	0.9 (1)	26 (32)	23 (32)	NA	NA	(+)	NA	(-)	(+)	NA	NA

TB=Total Bilirrubin – **AST**= Aspartate Aminotransferase – **ALT**= Alanine Aminotransferase – **PT= Protrombin- HAV** = Hepatitis A Virus- **IgM** / **IgG** = Immunoglobulin M/G- **HBsAG**= Surface Antigen of Hepatitis B Virus (HBV) — **HBeAG** = E Antigen of HBV – **Anti HBe** = Antibody to e Antigen – **Anti HBs** = Antibody to Surface Antigen – **HCV** = Hepatitis C Virus – **Ab** = Antododies – **VL** = Viral Load

DISCUSSION

After viral uptake, HBV is transported into the cell nucleus where it releases its genome. Its DNA is wrapped into a covalent close circular DNA (cccDNA) which is a reservoir of genetic information. [6]
In acute infections, there is a cytholitic effect which brings to hepatocytes death and cccDNA disappearance. On the other hand, chronic infection is associated with an impaired T cell response, and patients progress through different phases, numbered from 1 to 5: Phase 5 is characterized by: HBsAg negative, anti HBc positive, with or without presence of anti HBs. Aminotransferases levels are normal and HBV DNA usually is undetectable. [6]
As cccDNA is present in liver cells, immunosupression could lead to HBVr. The American Association for the Study of Liver Diseases (ASSLD) defines HBVr if the following criteria is fulfilled: a) a rise in HBV DNA compared to baseline (if available); b) sero-reversion from HBsAg negative to positive (for HBsAg negative) and c) Aminotransferases flare $\geq$ 3 times the baseline level. [7]
LFTs abnormalities may be present in COVID-19 patients, [3,8] but it is not clear whether liver injury is a consequence of the virus itself, if it reflects an inflammatory response with liver damage, or if it is caused by drug related toxicity (antibiotics, antipyretics, etc.). [9]
The incidence of CLD among COVID-19 patients is 0.6-37.6%. No evidence of higher risk of mortality is reported in patients with stable CLD without advanced fibrosis. [3,10] Viral hepatitis and fatty liver disease are the most frequent CLD, while other entities (autoimmune hepatitis, Primary Biliary Cholangitis, Wilson, etc) only account for less than 10% of them.
Recently a paper from the United Arab Emirates reported a case of HBVr in a patient with COVID-19 infection. The patient presented acute liver failure and tested positive for SARS-CoV2. Entecavir, lactulose and standard work out were done and full recovery was observed. [5]
Our patient presented HBVr 7 weeks after a mild COVID-19 infection. Usually HBVr is related to immunosuppressive treatment (systemic steroids, cytostatics, immunotherapy, monoclonal antibodies, etc) and patients are stratified in low, medium or high risk of reactivation according to: HBV serological status, immunosuppressive therapy (not only the drug class but also the period of time that it will be administered). [7] Antiviral prophylaxis or surveillance is recommended on those bases.
In 2015, our patient had an acute HBV which resolved spontaneously. Then he had a mild COVID-19 infection. He did not receive immunosuppressive drugs, convalescent plasma or any off label drug. Despite not being a high risk reactivation patient, HBVr was documented, and once Entecavir 0.5mg/day was started, his viral load became negative and liver function tests became normal.
It is unclear if SARSCoV2 infection triggered HBVr in this patient or if it was just a coincidence. However it draws attention that an acute HBV infection that occurred in 2015 and resolved spontaneously in an immunocompetent host, reactivates 5 years later in the context of a recent COVID-19 diagnosis. If HBVr was truly a consequence of a "viral interference" of SARS-CoV2, then we suggest that an increased attention should be paid to this kind of patients during pandemic.

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CONFLICT OF INTEREST

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