Case report

Can Hepatitis B virus (HBV) reactivation be the result of a mild Covid-19 infection with no need of systemic immunosuppressive therapy?

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Abstract: Hepatitis B virus reactivation (HBVr) is a well described result of immunosuppressive therapy initiation in a variety of diseases with dose and duration of treatment being the main factors determining the probability for reactivation. Such cases have been described also in Covid-19 patients treated with immunosuppressive therapies. Nevertheless, there have also been reported cases of Covid-19 infection that led to HBVr with no concurrent immunosuppressive therapy or any other described cause. In accordance with that observation, we present a patient followed for a period spanning 20 years with HBeAg negative chronic HBV infection and non-detectable HBV DNA who after a mild Covid-19 infection treated only with low dose and short duration inhaled corticosteroids (ICS), developed elevated AST and ALT as well as elevated HBV DNA levels. During the diagnostic workout other etiologies of abnormal liver biochemistries were excluded and thus the diagnosis of HBV reactivation was established and treated with entecavir. Since other causes of reactivation were excluded, and ICS dose and duration was found baring only a very low risk (<1%) for HBVr, Covid-19 infection could be considered the most probable cause of reactivation.

Keywords: HBV reactivation; Covid-19; immunosuppressive therapy

1. Introduction

Hepatitis B virus (HBV), part of the Hepadnaviridae family [3], is responsible for about 296 million chronic hepatitis infections according to latest World Health Organization (WHO) data [1]. Following HBV infection and based on the interaction between HBV and the host's immune system response, the acute infection can either resolve or progress to chronic hepatitis B [3]. Current nomenclature for HBV chronic infection marks the presence of five separate phases, not always as an infection sequence, but based on HBeAg seropositivity as well as serum levels of HBV DNA and alanine aminotransferase (ALT) [3]. Thus, the following phases arise: HBeAg (+) chronic HBV infection, HBeAg (+) chronic hepatitis B, HBeAg (-) chronic HBV infection, HBeAg (-) chronic hepatitis B and HBsAg-negative phase [2,3]. Common ground in chronic Hepatitis B or infection and regardless of the phase, is the persistent presence of the covalently closed circular DNA (cccDNA) inside hepatocytes nucleus [5]. It is cccDNA that acts as the template for HBV transcripts that are subsequently translated into the main proteins of the virus [3,4], remaining also the most important cause of HBV reactivation (HBVr) at any time and any phase especially under conditions of immunosuppression [6-9].

As of late 2019, Covid-19 pandemic has proved a serious global public health issue. The responsible virus itself -SARS-CoV-2 not only affects the respiratory system but as already reported in several studies it also causes liver injury with abnormal liver biochemistry [10,11,12,16]. Multiple

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possible liver injury mechanisms have been proposed, such as direct cytopathic effect of SARS-CoV-2 through angiotensin-converting enzyme 2 (*ACE2*) and transmembrane serine protease 2 (*TMPRSS2*) receptors of cholangiocytes and hepatocytes [13]. Other mechanisms include liver injury caused by severe inflammation, hypoxia, toxicity of the drugs used for Covid-19 treatment and vascular changes attributed to coagulopathy [14,15].

Taking into consideration that both HBV and SARS-CoV-2 can potentially cause liver injury, several studies attempted to investigate coinfection cases and highlight the effect of the latter on chronic HBV natural history on one hand, and the effect of HBV seropositivity on the severity of Covid-19 infection on the other hand [17]. Attempting to help address this controversial matter we report a case of a patient presenting with HBV reactivation soon after Covid-19 infection without administration of systemic immunosuppressive medication.

2. Case report

A 49-year-old female presented in the outpatient Department with elevated serum AST and ALT level. The patient has been followed for HBeAg negative chronic HBV infection every six months for twenty years presenting always normal liver enzymes and non-detectable HBV DNA Apart from that, patient's prior medical history did not include any other health problem in need of long-term medical treatment, while no alcohol consumption, no medications over the counter and no smoking was mentioned.

The patient reported symptoms indicative of respiratory tract infection 3 weeks prior to her presentation. She was tested positive for Covid-19 infection and due to mild symptoms only a combination of budesonide 160 μg plus formoterol fumarate dehydrate 4.5 μg, for a duration of five days were prescribed. Over the course of SARS-CoV-2 infection, the patient experienced no complications and had no need of hospitalization or further treatment.

At her first hepatology consultation appointment, apart from abnormal liver chemistries, the patient experienced no other symptoms. More specifically, in the blood tests presented by the patient, aminotransferases were mildly elevated with AST level double the upper limit of normal (ULN) and ALT level triple the ULN (Table 1). No other important deviations from normal were noted in the blood tests presented (Table 1). Liver and hepatitis panel tests as well as upper abdominal ultrasound were prescribed and at her second appointment, one week later, the patient presented with the results. Persisting elevated AST and ALT levels double and triple the ULN respectively were observed (Table 1). As for her Hepatitis B known status the patient was HBsAg-positive, HBeAg-negative, anti-HBe-positive and anti-HBC–positive with HBV-DNA at 9.350.000 iu/ml.

Table 1. Blood test results.

	1st consultation	2nd consultation	2 months after entecavir
AST (U/L)	82	71	28
ALT (U/L)	106	90	30
ALP (U/L)	106	80	84
γGT (U/L)	16	19	20

Moreover, the patient was tested negative for anti-HCV antibodies, anti-HDV antibodies, antinuclear antibodies (ANA), antimitochondrial antibodies (AMA), anti-smooth muscle antibodies (ASMA) and anti-dsDNA antibodies (Table 2). Immunoglobulin levels showed no deviation from normal (Table 2). The upper abdominal ultrasound revealed no abnormalities and alpha-fetoprotein (a-FP) levels were normal. Abnormal liver chemistries were attributed to HBV reactivation and thus entecavir was prescribed.

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Table 2. Trend over time of HBV serologic markers, anti-HCV and anti-HDV.

	Prior six months	2nd consultation	2 months after entecavir
HBsAg	+	+	
HBeAg	-	-	
Anti-HBc	+	+	
Anti-HBe	+	+	
Anti-HCV	-	-	
Anti-HDV	-	-	
HBV DNA (IU/ml)	Non-Detectable	9.350.000	54.000
IgG (mg/dl)		1555	

Two months after the initiation of entecavir, AST and ALT levels had normalized (Table 1) whereas HBV DNA levels demonstrated a decreasing trend (Table 2). The patient remains asymptomatic under close surveillance.

3. Discussion

We present a case of HBV reactivation (HBVr) in a female patient with a 20-year history of chronic HBeAg negative HBV infection occurring after a mild Covid-19 infection. Usually, HBVr occurs when the host immune system loses the ability to suppress the virus replication [24]. Both HBsAg-positive/anti-HBc-positive and HBsAg-negative/anti-HBc-positive patients preserve the potential of HBVr [25] under certain circumstances. These comprise either concomitant use of immunosuppressive therapies or variable viral interactions. Such interaction is well described in HBV/HCV coinfection cases, where HCV usually suppresses HBV replication leading to low levels of HBV DNA [39-42]. Consequently, a Direct-Acting antiviral (DAA) therapy aiming for sustained virologic response (SVR) of HCV infection may lead to HBV reactivation in cases where no concurrent nucleoside/nucleotide analogue (NA) HBV therapy is applied [39,40].

Regarding the definition of HBVr a variety of variants have been proposed and used in different studies [23]. We used the latest proposed nomenclature presented by Papatheodoridis, et al. (2022), at their latest systematic review, meta-analysis, and expert opinion [6]. Accordingly, our patient with a known chronic HBV infection (HBsAg-positive) diagnosed 20 years ago that was currently found with elevated levels of HBV DNA ≥ 10.000 IU/ml, met the proposed criteria for HBVr [6].

In our patient, to ensure the accuracy of HBVr diagnosis, other causes of viral hepatitis such as HAV, HEV, HCV and HDV were excluded. Moreover, a diagnostic workup for other etiologies of abnormal liver biochemistry such as autoimmune hepatitis (AIH) and Primary Biliary Cholangitis (PBC) using non-organ specific autoantibodies such as ANA, ASMA and AMA was carried out [18-20]. Imaging with upper abdominal ultrasound was also used to rule out focal liver lesions as a cause for elevated AST and ALT in combination with normal levels of a-FP [21,22].

Following the establishment of the diagnosis of HBVr, the main question arising concerned the pathophysiology of HBVr 20 years after the initial diagnosis. In general, the main reason leading to impaired ability to suppress HBV replication and thus to a possible reactivation is the initiation of immunosuppressive treatment [6,23]. A broad spectrum of immunosuppressants has been incriminated for HBVr [23]. Among others, corticosteroid treatment for any indication including Covid-19 has been in the spotlight of studies investigating its ability to induce HBVr [26-28]. This ability is brought about by the activation of a DNA sequence known as Glucocorticoid Response Element (GRE) enclosed in HBV genome on one hand [29], and by immunosuppressive properties of corticosteroids on the other hand [23]. Nevertheless, reactivation probability depends on the dose and treatment duration of corticosteroids [6,23]. The American Gastroenterological Association addressed this matter [23] by categorizing the HBVr risk induced by immunosuppressants as high when the risk of reactivation is expected to be more than 10%, moderate when frequency of reactivation is between 1% and 10% and low when reactivation risk is < 1%. Thus, for HBsAg-positive patients a moderate (10–20 mg) or high (>20 mg) dose of prednisone (or equivalent) for ≥ 4 weeks results in a high risk for HBVr, a low dose (<10 mg) of prednisone (or equivalent) for ≥ 4 weeks results in a moderate risk for

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HBVr while corticosteroid therapy for ≤ 1week results in low risk for HBVr [23]. Moreover, a dose >20mg for a treatment duration >2 weeks results in significant immunosuppression [30].

In our patient, as already mentioned, the course of Covid-19 infection was mild and as a result only inhaled budesonide 160 μg plus formoterol fumarate dehydrate 4.5 μg, for a five-day duration was prescribed. Could this possibly be the reason of HBVr in our case? Data regarding inhaled corticosteroids (ICSs) derive from studies addressing their efficacy and safety profile especially in asthma and chronic obstructive pulmonary disease. In general, ICS's action is mainly applied locally at the airway level and is effective in low doses [31]. Apart from that, according to a study from Maijers et.al. (2020) an increase of 1000 μg of fluticasone propionate is commensurate with 5mg of prednisone, while 1000 μg of budesonide is commensurate with 2mg of prednisone [32]. Thus, even the high doses used in severe respiratory disorders such as budesonide dose of up to 1600 μg/day or fluticasone propionate dose of up to 1000 μg/day [32] correspond to low dose (<10mg) of prednisone. As a result, HBVr risk with ICS courses administered for less than a 1week, as in our patient, is lower than 1%.

As ICS administration did not seem to explain the sudden HBVr of our patient, a review of the literature was carried out in order to investigate the possibility of HBVr induced by Covid-19. Most cases of HBVr after SARS-CoV-2 infection were attributed to immunosuppressive treatment such as dexamethasone 6mg per day [5], other systemic corticosteroids like methylprednisolone 40mg per day [17,34] or tocilizumab which was used in severe cases of Covid-19 [35]. The aforementioned systemic corticosteroid doses correspond to a high dose of prednisone (40mg of prednisone equivalent for dexamethasone and > 40mg of prednisone equivalent for methylprednisolone) [36] that even when administered for <7 days, can result in increasing risk for hepatitis flare [27,33].

Interestingly enough, we also came across patient cases where Covid-19 was considered to be the trigger for HBVr with other causes of reactivation excluded [14,17,37,38]. The pathogenesis pathway for this reactivation in patients with HBV and SARS-CoV-2 coinfection remains to be elucidated, but the disruption of the balance of immune system activity on one hand and HBV replication on the other has been proposed as a possible mechanism [14].

4. Conclusions

In conclusion, due to the low risk for HBVr provoked by ICS, and in accordance with other cases presented, our patient's HBVr was attributed to the recent Covid-19 infection, underlining the need for close monitoring of patients who are HBsAg -positive in case of infection with SARS-CoV-2, even when no systemic immunosuppressive treatment is administered. In order to answer the question if HBVr may be the result of viral interaction with a non-hepatotropic virus like SARS-CoV-2 more research is needed.

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