AN UNUSUAL CASE OF HBV REACTIVATION IN A PATIENT WITH CHOLANGITIS AND CHOLEDOCHO-LITHIASIS UNDERGONE TO ERCP. A CASE REPORT

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ABSTRACT

Introduction*: In the landscape of presentation of HBV infection, it is possible to identify patients with Hepatitis B "e" Antigen-positive chronic hepatitis B infection without liver disease (previously called "asymptomatic chronic carrier"), and in the natural history of this condition an Hepatitis B Virus reactivation is possible. In literature it has been shown that reactivation often occurs during conditions of immunosuppression or chemotherapy, although in recent years case reports of Hepatitis B Virus reactivation are emerging in chronic coinfected patients after therapy with Direct Acting Antivirals.*

Materials and methods*: We describe a clinical case of Hepatitis B Virus HBV reactivation not ordinarily secondary to immunosuppression or chemotherapy, but realistically secondary to choledocholithiasis. It has been supposed an atypical reactivation of HBV, and therefore an antiviral treatment with entecavir has been promptly initiated.*

Results*: At 24 weeks and one year after the antiviral treatment, the patient showed a normalization of all liver function tests and an undetectable HBV DNA with Polymerase Chain Reaction test.*

Conclusion*: In case of liver dysfunction in a patient with an history of HBV infection, we suggest to firstly suspect and test a viral reactivation and then, if the reactivation is confirmed, to start the antiviral therapy as early as possible. It would be also desirable to evaluate the extension of the pre-treatment protocols with 3rd generation Nucleos-(t)ide analogues even in the case of important septic episodes, major surgery and invasive procedures.*

Keywords: *Hepatitis B Virus reactivation, cholangitis, choledocholithiasis, endoscopic retrograde cholangiopancreatography, entecavir, Nucleos(t)ide analogue.*

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Introduction

Hepatitis B Virus (HBV) chronic infection, which is often under-recognized, is a very prevalent healthcare problem, indeed there are about 350 million of people infected worldwide[(1)]. These data are confirmed in our geographic area (South Italy) where statistics highlights a considerable part of population as HBsAg-positive, not rarely unaware of their condition[(2)].

In the landscape of presentation of HBV infection, it is possible to identify patients with chronic infection (HBsAg-positive or anti-HBc-positive) without liver disease, and in the natural history of this condition an HBV reactivation is possible.

HBV reactivation is a condition potentially life-threatening, characterized by:

• increase of liver function tests, especially AST (aspartate aminotransferase) and ALT (alanine aminotransferase),

and/ or

• the appearance or increase of HBV-DNA detectable blood levels[(1)].

Usually HBV reactivation occurs in HBsAg positive patients, following chemotherapy with steroids or rituximab (especially after hematological

malignancies or breast cancer), or after immunosuppression (anti-tumor necrosis factor a - TNFa - or other drugs for Rheumatoid Arthritis or Inflammatory Bowel Disease). Nonetheless, in recent years, case reports of HBV reactivation are emerging in chronic co-infected patients when HCV is cleared after treatment with direct-acting antivirals (DAAs), the current standard of care in HCV infected patients at all stages of disease[3,4,5,6,7,8].

However, in literature cases of spontaneous reactivations are also reported, and may be related to patient's individual peculiarities, such as comorbidities, age and sex, but may be also correlated with intrinsic viral characteristics of HBV, for example mutations able to influence the viral recognition by the immune system[9].

An impaired immune function seems to be a key factor that leads these patients to the development of viral reactivation. Different clinical predictors of reactivation of HBV have been identified, including the level of serum HBV DNA prior to immunosuppression, the type of cancer undergoing to chemotherapy regimen, and the intensity of immunosuppression itself.

The rate of reactivation of HBV varies from 20% to 50% according to the data of literature[1]. However, it is supposed that virologic characteristics of HBV could contribute to the reactivation in immunocompromised patients[10].

Case report

In this case report we describe a clinical case of HBV reactivation not secondary to immunosuppression or chemotherapy, but realistically secondary to cholangitis and choledocholithiasis.

Our Patient: a 65-year old male who had been taken in charge by the Surgery Unit of our Hospital with a symptomatology arisen three days before and characterized by:

- abdominal pain, localized to the upper quadrants, especially in epigastrium and in right ipocondrium,
- jaundice,
- vomit,
- fever.

Anamnesis showed arterial hypertension and past HBV infection.

The patient was previously under the care of another Hepatology Unit for his hepatologic condition of inactive carrier state. Last data given us by the patient showed the following results: AST 22 U/L, ALT 24 U/L; HBV DNA 1870 IU/l, Total Bilirubin 0.90 mg/dl, HBsAg Index 1=4500, HBsAb Index=0.9, HBcAb Index=6, HBeAg Index=3.90, HBeAb Index=0.1, anti-HDV IgG/IgM=Negative, Anti-HCV=Negative.

Liver ultrasonology, performed 10 months before, showed: moderated steatosis, biliary sludge, microlithiasis, absence of lesion suggestive for neoplasm.

The patient had not been previously subjected to treatment with corticosteroids, immunosuppressive and/ or immunomodulator drugs or anticancer drugs.

On admission, laboratory results were as follows: white blood cells (WBC) 14500/ml; Hemoglobin (Hb) 12.5 g/dL; platelets 140,000/ml; creatinine 1.0 mg/dl; total bilirubin 18.1 mg/dL, direct bilirubin 10.8 mg/dL, aspartate aminotransferase (AST) 70 IU/L, alanine aminotransferase (ALT) 59 IU/L, increase of gamma-GT (280 U/L) levels, while amylase and lipase were normal.

The patient was treated with: NaCl saline solution 0.9% and glucose solution 5% (1000 ml in 24 h) i.v (intravenous); levofloxacin 500 mg i.v. every 12 hours, ceftriaxone 1 g. every 24 hours i.v., omeprazole 40 mg/day i.v., diclofenac 75 mg intramuscular (i.m.), butylscopolaminium i.m. and metoclopramide i.m.

Considering the clinical situation, the Surgeons proceeded with further investigation, especially with abdominal ultrasound, computed tomography (CT) and cholangio-magnetic resonance (MRI). These exams showed dilatation of the biliary intrahepatic and common bile duct (15 mm) with at least three gallstones in gallbladder. After that, the patient underwent the endoscopic retrograde cholangiopancreatography (ERCP) performed with sphincterotomy/ papillotomy.

After a few days, despite the ERCP, the clinical and laboratory data showed no apparent resolution (AST 74 IU/l, ALT 68 IU/l, total bilirubin 15.6 mg/dl, direct bilirubin 6.4 mg/dL). It was also repeated the cholangio-MRI that excluded a residual choledocholithiasis.

The patient was then referred to our Hepatology Unit, and in consideration of the anamnestic condition of HBeAg-positive chronic hepatitis B infection without liver disease, we performed the research of serological markers of HBV again, which highlighted: HBsAg positive (8880.00 IU / ml), HBsAb negative, positive HBcAb.

Moreover, the level of HBV DNA amounting to 3.600.000 IU/ml showed a clear increase compared to the last data available (1870 IU / l).

It was then assumed an atypical reactivation of HBV, and therefore an antiviral treatment with entecavir was promptly initiated at a dosage of 0,50 mg per day.

A month after the beginning of treatment with entecavir, the serum ALT and AST were normalized (ALT=34 U/L, AST =16 U/L) and the amount of HBV DNA was reduced to 12.000 IU/ml.

At 24 weeks, the patient showed normalization of all liver function tests and HBV DNA undetectable.

One year after the antiviral treatment, our follow-up examination showed the following serological data: HBsAg positive, HBsAb and HBeAg positive, HBeAb negative, HBcAb positive, HBV DNA was undetectable with Real-Time PCR method.

After two years, ALT and AST were normal, HBV DNA was undetectable, HBsAg positive, HBcAb positive, HBeAg positive, HBeAb negative. There were not adverse events occurred during or after therapy with tenofovir.

After four years, ALT and AST were normal, HBV DNA was undetectable, HBsAg positive, HBcAb positive, HBeAg negative, HBeAb negative. There were not adverse events occurred during or after therapy with tenofovir. The exams showed us an initial feature of seroconversion, therefore the therapy was successful (Fig. 1and Tab. 1).

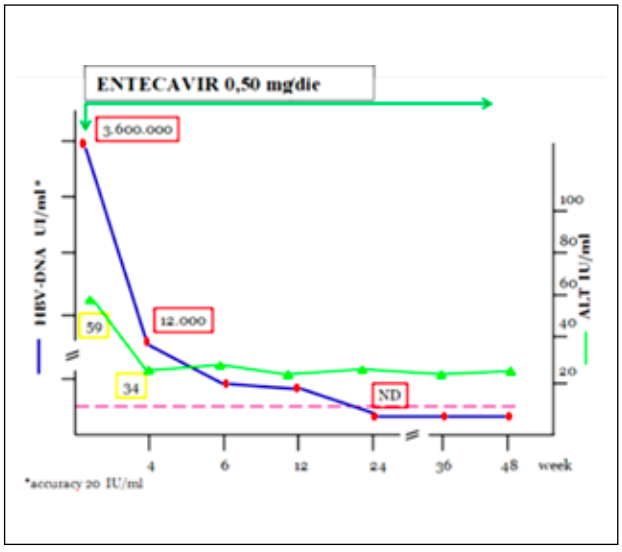

Figure 1. Normalization of ALT and breakdown of HBV-DNA copies. Legend: ND=Not Detected (accuracy IU/ml).

Legend: ND=Not Detected (accuracy IU/ml). Therapy with entecavir 0.50 mg / day resulted in the rapid reduction of serum levels of HBV-DNA until non-detectable and consequently the normalization of ALT.

Discussion and conclusions

Because of the virologic peculiarity of HBV, the infection may be heterogeneous. It has been established that HBV is capable to integrate his DNA into genetic matter of the host cell also in the early phase of an acute infection. Then, it was uncovered the existence of a covalently closed circular form of the DNA of the virus (cccDNA) that persists for decades in the hepatocytes of patients with acute hepatitis solved and serves as a template for the transcription of new copies of the virus[11].

This explains why viral flare can occurs frequently during the natural history of disease as an expression of the conflict between the attempts of HBV replication and immune surveillance.

Reactivation of HBV is however associated with the presence of diseases that can compromise the normal function of the immune system or the use of immunosuppressive treatments.

Indeed, patients most frequently affected by HBV reactivation are those patients undergoing to:

• chemotherapy for solid neoplasms, but especially hematological neoplasm;

• biological therapies for lymphoma as rituximab (anti CD-20), infliximab (and other anti-TNF alpha drugs) or steroids;

• immunosuppressant drugs for inflammatory bowel disease, skin diseases or rheumatoid arthritis.

In recent years, the increase in the intensity of immunosuppression due to a broader use of chemotherapy drugs and innovative drugs, such as the monoclonal antibodies, has brought to the fore the problem of HBV reactivation[12].

Reactivation can be transient and clinically silent, or can gradually lead to cirrhosis, but often causes an acute worsening of the disease that can also lead to fulminant hepatitis. The importance of HBV reactivation is its potential severity, so it is very important to prevent its occurrence through the screening of people at risk, and subsequently with the appropriate antiviral therapy. Generally, the mechanism underlying such exacerbations and reactivations is largely related to immunosuppression and/or to the hepatocellular damage effects of the immune-suppressive drugs[13,14].

Studies of immunological mechanisms have made it clear that the liver injury secondary to viral reactivation is a two-stage process. The first step begins when cytotoxic therapy and/or immunosuppressive therapy are set up; this therapy directly stimulates the HBV replication and causes

an increase in serum levels of HBV-DNA, HBsAg and HBeAg, with a significant increase of infected hepatocytes[1,13,14].

	Pre-ERCP	Post-ERCP	ETV 0,50 mg/die	4W	6W	12W	24W	36W	48W	60W	72W	84W	192W
RBC 10^6micr/L	5.10	5.00		5.150	5.180	5.25	5.20	5.40	5.25	5.18	5.30	5.50	5.49
WBC 10^3micr/L	14.50	13.00		8.0	7.0	6.5	6.5	7.2	6.0	5.8	5.5	6.2	6.6
PLT 10^3micr/L	140	146		180	175	170	180	176	180	185	175	180	178
Hb g/dL	12.5	12.0		13	14	14.5	15.5	15	14.9	15	16	15.6	16.1
AST U/L	70	74		32	30	28	20	22	20	19	19	20	17
ALT U/L	59	60		34	32	22	24	26	22	20	23	22	16
G-GT U/L	280	198		50	38	26	24	24	22	24	20	20	18
TB mg/dL	18.1	15.6		1.50	1.30	1.00	0.9	1	1..6	1.9	1.8	2.5	2.2
DB mg/dL	10.8	6.4		0.90	0.90	0.60	0.60	0.7	0.4	0.5	0.5	0.6	0.3
Tot.Prot. g/dL	5.80	5.00		6.20	6.30	6.80	6.40	6.90	6.7	6.7	6.9	6.8	6.7
INR	1.1	1.0		1.0	1.0	1.0	0.9	1.0	1	1.1	1.0	1.0	1.1
HBsAg Index [1]	4500	8880		4350	4380	4200	4248	3850	3950	3500	2850	3000	4028
HBsAb IU/L [2]	0.9	0.9		0.8	0.7	0.8	0.9	0.8	0.8	0.9	0.9	1.0	0.0
HBcAb Index [3]	6	6		4	6	6	5	5	4	5	5	4	8.3
HBeAg Index [4]	3.90	4.50		4.00	4.10	3.80	3.17	3.20	3.80	2.80	2.00	1.1	ND*
HBeAb Index [5]	0.1	0.1		0.2	0.2	0.1	0.2	0.2	0.1	0.4	0.8	0.	ND*
HBV-DNA IU/ml	1900	3.600.000		12.000	6.000	2.000	ND*	ND*	ND*	ND*	ND*	ND*	ND*
Anti-HDV IgG/IgM	*ND	*ND		*ND		*ND							
Anti-HCV	*ND	*ND		*ND		*ND							
Anti-HIV	*ND	*ND		*ND		*ND							

Table 1. Complete hemo-chemistry panel. Follow-up data of the laboratory tests and HBV markers from the start point of ERCP to finish point of the Entecavir (ENT) treatment.

Legend:

1 HBsAg Index <0.9 negative, 0.9-1.1 borderline, >1.1 reactive

2 HBsAb IU/L <9 negative, 9-11 bordeline, >11 reactive

3 HBcAb Index <0.9 negative, 0.90-1.0 borderline, >1.0 reactive

4 HBeAg Index <0.9 negative, 0.9-1.0 borderline, >0.9 reactive

5 HBeAb Index <1.1 negative, 0.9-1.1 borderline, >1.0 reactive

**ND=Not Detected (accuracy IU/ml)*

The second step occurs instead after reduction or discontinuation of therapy; in this phase, the restoration of the immune function often runs through a rebound of the inflammatory response and cell mediated cytotoxic activity, which causes a rapid immune-mediated cytolysis of infected hepatocytes with consequent flare of transaminases[1,13,14].

The characteristic of our case is the event triggering the reactivation is not an immunosuppressive therapy or a neoplastic disease.

Therefore, it is reasonable to assume that in this case the reactivation was caused by at least two equally prominent factors: acute calculous cholecystitis and ERCP.

It is well known as in Acute Cholecystitis, and also in Acute Pancreatitis (A.P.), there is an activation of local inflammatory cells and various inflammatory mediators[15,16]. Localized inflammation is the body's initial physiologic protective response, which is generally strictly controlled at the site of injury. Loss of the local control results in excessive uncontrolled activation of inflammatory cells and mediators. This response is defined as systemic inflammatory response syndrome (S.I.R.S). Pro-inflammatory cytokines, such as tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β), are released via portal vein; in addition, the production of cytokines enhances pro-inflammatory signals, and IL-6 stimulates the synthesis of acute phase proteins in the liver that becomes the leading actor of early inflammatory response. As described by Kylänpää[15], in the course of Acute Pancreatitis there is a concomitantly systemic inflammation with rapidly-strengthening compensatory anti-inflammatory response syndrome (C.A.R.S.). Usually an anti-inflammatory response may be sufficient to control the systemic inflammatory reaction, and it is a sign of good prognosis, but C.A.R.S. may be excessive, leading to immune deficiency or immunosuppression, which makes the host susceptible to secondary infections.

In immunosuppression, monocytes show impaired antigen presentation capability, due to IL-10 production, and a deep reduction of their ability to produce proinflammatory cytokines. All these phenomena, which occur also in acute abdominal inflammation, could explain, at least partially, the pathophysiology of our strange reactivation case. Indeed, the early inflammatory phase could play as a trigger, emphasizing metabolic function of hepatocytes; the immunomodulatory phase could represent the window for the loss of immune-surveillance and the following HBV replication.

Later, the immune recovery would cause a liver damage due to the hepatocellular lysis[15,16,17].

On the report of this clinical experience and according to what is reported in literature, we should pay more attention to the health status and immune competence of patients with HBV.

In the case of HBV infection, immunodeficiency, although temporary, could allow opportunities for replication to the virus, which if not controlled could lead to an active infection and even to a hyperacute fulminant hepatitis with acute liver failure, need for transplant and high risk of death for the patient.

Ultimately, we can argue that a trigger factor able to modify the function of the immune system, may represent a potential opportunity to start HBV reactivation, and this can lead to severe hepatic dysfunction, up to acute liver failure and sometimes to exitus.

Currently, there is not consensus or guidelines concerning the use of antiviral therapy in patients undergoing major surgery or during inflammatory/septic events.

However, if our case data will be confirmed in the literature, it might be reasonable to suspect and test a viral reactivation in case of liver dysfunction in a patient with HBV infection[1,18,19,20]. Moreover, if reactivation is confirmed, it could be useful to start treating the patient as early as possible. It would be also desirable to conduct studies and more thorough analysis regarding the uncommon reactivation trigger events, and possibly to evaluate the extension of the protocols of pretreatment with 3rd generation NUCs even in the case of important septic episodes, major surgery and invasive procedures[1,20].

Key messages

The current international guidelines and consensus do not suggest prophylaxis with NUC in HBeAg-positive chronic hepatitis B infection without liver disease undergoing invasive procedures or with ongoing severe infection to avoid a possible reactivation. However, if other clinical cases, such as the one we have described, will be reported, and/or if our data will be confirmed in large series, it could be reasonable to consider the extension of prophylaxis with NUC in this category of patients. In our opinion, in chronic HBV infection without liver disease who develop a serious infection or who are undergoing invasive procedures, it could be important to recommend ALT and possibly a close monitoring of serum HBV-DNA level in order to promptly detect a possible reactivation of HBV and early initiation of treatment with NUC.

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List of abbreviation
HBV: Hepatitis B Virus
NUCs: Nucleos-(t)ide analogues
ERCP: Endoscopic Retrograde Cholangiopancreatography
DAAs: Direct-Acting Antivirals
PCR: Chain Reaction
AST: Aspartate Aminotransferase
ALT: Alanine aminotransferase
RBC: Red Blood Cells
WBC: White Blood Cells
Hb: Hemoglobin
PLT: Platelets
gamma-GT: gamma Glutamyl Transpeptidase
i.v.: intravenous
i.m. : intramuscular
CT: computed tomography
MRI: Cholangio-Magnetic Resonance
A.P.: Acute Pancreatitis
S.I.R.S: Systemic Inflammatory Response Syndrome
C.A.R.S.: Compensatory Anti-inflammatory Response Syndrome
TNF-α: Tumour Necrosis Factor-alpha
IL-1β: Interleukin-1β
IL-10: Interleukin-10
ENT: Entecavir
TB: Total Bilirubin
DB: Direct Bilirubin
INR: International Normalized Ratio

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