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Spontaneous hepatitis B surface antigen seroconversion after long lasting hepatitis B virus infection in a chronic hemodialysis patient

Spontana HBsAg serokonverzija nakon dugogodišnje infekcije virusom hepatitisa B u pacijenta na kroničnoj hemodijalizi

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Abstract. ***Aim:*** The aim was to present an unusual spontaneous disappearance of HBsAg after a long-lasting infection. ***Case report:*** A 26-year-old man started chronic hemodialysis (HD) in 1994 for chronic glomerulonephritis. Serological analysis was positive for hepatitis B virus (HBV) infection. During the following years he was treated with HD and his HBV markers remained unchanged (HBsAg positivity). When antiviral therapy became available the patient refused to be treated. In 2006 his HBsAg was negative for the first time in 12 years, while anti-HBs and anti-HBc were positive, which would indicate that he became immune late after a natural infection. To date, all repeated check-ups have been negative for HBsAg. In 2008 he received a kidney transplant from a deceased donor and was put on immunosuppressive (IS) therapy. During the IS treatment, which is still ongoing, he was stable and without HBV viremia (HBsAg-negative). ***Conclusion:*** It still remains unclear how spontaneous HBsAg seroconversion happened in our patient after a long lasting infection. It is also interesting that 11 years after seroconversion his HBV markers are still unchanged (HBsAg negative) and show signs of a resolved HBV infection, even though he has been immunosuppressed due to kidney transplantation for already 9 years. It is possible that his anti-HBs levels are high enough to protect him and inhibit HBV reactivation or the virus has not been dormant in his hepatic cells at all.

Key words: HbsAg; hemodialysis; hepatitis B virus; immunosuppression; kidney transplantation; seroconversion

Sažetak. ***Cilj:*** Cilj je prikazati neobičan spontani nestanak HBsAg nakon dugotrajne infekcije. ***Prikaz slučaja:*** Dvadesetšestogodišnji muškarac započeo je kroničnu hemodijalizu (HD) 1994. godine zbog kroničnog glomerulonefritisa. Serološka analiza bila je pozitivna na infekciju virusom hepatitisa B (VHB). Tijekom sljedećih godina liječen je HD-om i njegovi su biljezi VHB-a ostali nepromijenjeni (HBsAg pozitivnost). Kada je antivirusna terapija postala dostupna, pacijent je odbio liječenje. HBsAg postao je 2006. negativan prvi put u 12 godina, dok su anti-HBs i anti-HBc postali pozitivni, što bi upućivalo na to da je nakon prirodne infekcije razvio imunost. Do sada su sve ponovljene pretrage negativne za HBsAg. 2008. godine transplantiran mu je bubreg od mrtvog darovatelja i uvedena terapija imunosupresivima (IS). Tijekom liječenja IS-om, koje je u tijeku, bio je stabilan i bez HBV viremije (HBsAg negativno). ***Zaključak:*** Još uvijek nije jasno kako se spontana HBsAg serokonverzija dogodila u našeg pacijenta nakon dugotrajne infekcije. Također je zanimljivo da su i 11 godina nakon serokonverzije njegovi biljezi VHB-a još uvijek nepromijenjeni (HBsAg negativnost) i pokazuju znakove preboljele infekcije VHB-om, unatoč devetogodišnjem IS-u zbog bubrežnog presađivanja. Moguće je da su njegove razine anti-HBs dovoljno visoke da ga zaštite i inhibiraju reaktivaciju VHB-a ili virus uopće nije prisutan u njegovim hepatocitima.

Ključne riječi: HbsAg; hemodijaliza; hepatitis B virus; imunosupresija; serokonverzija; transplantacija bubrega

Comment: This case report won the award for best conference paper according to *Medicina Fluminensis* at the first International Biomedical Student Congress Rijeka 2017 (2 – 4 November 2017, Rijeka, Croatia).

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INTRODUCTION

Currently, around 400 million people worldwide live with chronic hepatitis B virus (HBV) infection and 500.000 people will probably die each year as a result of liver disease caused by HBV[1]. Clinical spectrum of HBV infection ranges from subclinical to acute symptomatic hepatitis or, rarely, fulminant hepatitis during the acute phase, and also from an inactive hepatitis B surface antigen (HBsAg) carrier state to chronic hepatitis, cirrhosis, and its complications during the chronic phase[2-3]. "Chronic carrier" of HBV is defined by the presence of HBsAg in serum for more than six months[4-5]. Some persons are able to mount a sufficient immune response and enter the third inactive carrier state, in which individuals are positive for HBsAg, clear HBV envelope ("e") antigen (HBeAg), develop antibodies against HBeAg (HBeAg seroconversion), while usually having low levels of HBV deoxyribonucleic acid (DNA) and normal alanine aminotransferase[6-7]. With regard to the meaning of the seroconversion, HBsAg seroclearance has been defined as the loss of serum HBsAg on two occasions at least six months apart[8]. The aim of our case report is to present an unusual spontaneous disappearance of HBsAg after a long-lasting infection, sustained even with immunosupression (IS) for kidney transplantation (TX).

CASE REPORT

A 13 year-old male patient was hospitalized for albuminuria in 1981. In 1987 at the age of 19 he was hospitalized again. The kidney biopsy was done and he was diagnosed with Glomerulonephritis mesangiocapillaris. In 1994 at the age of 26 he started chronic hemodialysis (HD) for chronic glomerulonephritis. By that time he received four doses of blood transfusion. In 1994 his serology test was positive for HBV infection. His HBsAg and antibodies against HBV core antigen (anti-HBc) were positive with negative anti-HBs. During the following years he was treated with HD and his HBV markers (HbsAg-positive) remained unchanged for years. When antiviral therapy became available, the patient refused to be treated with it. In 2006 his HBsAg was negative for the first time in 12 years period, while anti-HBs was positive, which indicated that he had become immune after a long lasting natural infection. To date, all repeated check-ups have been negative for HBsAg. The most recent one was done in 2016. In 2008 he received a kidney transplant from a dead donor and was put on IS therapy which consisted of prednisone, cyclosporin A (CsA) and mycophenolate mofetil. By that time and thereafter, his transaminases were within the referent range. His CsA blood levels were around 70 ng/L. His kidney graft function was good and stable during the whole follow-up time (creatininaemia around 140 µmol/L).

During his IS treatment, which was ongoing in 2017, he was stable and without HBV viremia

Spontaneous HBs antigenemia conversion after long-term infection with hepatitis B virus is rare but possible.

Table 1. Patient's hepatitis B markers

Date	HBs Ag	Anti HBs	Anti HBc	HBc Ag	Anti HBe	HBe Ag	HBV DNA
1987	/	/	/	/	/	/	/
1994	+	-	+	/	/	/	/
2004	+	+	+	/	+	-	/
2006	-	+	+	/	+	-	* sent to Zagreb, never done
2007	-	+	+	/	+	-	/
2008, april	-	+	+	/	+	/	/
2008, july	-	+	+	/	+	/	/
2009	-	+	+	/	+	/	/
2016	-	+	+	/	+	-	/

+ positive; – negative; / not defined

(HBsAg-negative). Complete available HBV markers are provided in Table 1.

DISCUSSION

Chronic HBV infection is a serious public health problem because of its worldwide prevalence and potential to cause other adverse consequences such as cirrhosis and hepatocellular carcinoma[9]. Annual rates of spontaneous HBsAg seroclearance in patients with chronic HBV infection have been estimated from 0.5 % to 2.2 %[10].

With long-term immunosuppression after renal transplantation, it is possible that no hepatitis B reactivation occurs, indicating the real protective role of anti-HBS antibodies even upon immunocompromised state as well as the likelihood of a complete disappearance of HBV from hepatocyte as a result of seroconversion.

The natural history of chronic HBV infection can be divided into 3 phases. The first phase, the immune tolerance phase, is characterized by active HBV viral replication. The second phase is the immune clearance phase and consists of hepatic inflammation followed by decreasing serum HBV DNA levels, a phase that varies greatly in frequency and duration. Finally, some persons are able to mount a sufficient immune response and enter the third inactive carrier state, in which individuals are positive for HBsAg, clear HBeAg, and develop antibodies against HBeAg (HBeAg seroconversion), while usually have low levels of HBV DNA with normal alanine aminotransferase blood levels[9]. There have been very few publications about spontaneous seroconversion in chronic HBV patients on HD. Patel et al. reported a case of a 62-year-old African-American woman who was HBsAg-positive at the time she started HD and remained so until 10 years later when she became HBsAg-negative followed by the development of anti-HBs. Prior to her seroconversion, she suffered a persistent infection of her HD arteriovenous graft that required prolonged antibiotic therapy and several surgical procedures. Their theory was that seroconversion was the result of a sufficient immune stimulation to allow successful seroconversion[11]. In our case the patient did not suffer any arteriovenous fistula or other infection by the time of the seroclearance that could trigger such an immune stimulation. As stated previously, HBsAg seroclearance has been defined as the loss of serum HBsAg on two occasions at least six months apart[8]. Patients who become HBsAg-negative and develop antibody to HBsAg are diagnosed as having resolved hepatitis B[12]. HBsAg seroclearance is an uncommon phenomenon in chronic HBV infection. During this "silent HBV infection" period HBV DNA may still be detectable by polymerase chain reaction in serum and more often in the liver[13]. Some individuals will spontaneously clear HBsAg, which usually confers a good prognosis if there is no pre-existing hepatocellular carcinoma or cirrhosis by the time of HBsAg seroclearance[9]. Nowadays, there is an universal consensus that all HbsAg-positive candidates for kidney TX should receive antiviral therapy with nucleos(t)ide analogues shortly before or at the time of grafting in order to maintain undetectable serum HBV DNA[14]. Our patient refused to be treated with antiviral therapy when it became available, which rules out seroconversion due to antiviral therapy.

In the research done by Rehermann et al. it was reported that HBV cccDNA (covalently closed circular DNA) can be present in hepatocytes and circulating peripheral mononuclear cells following clinically resolved infection[15]. Therefore, even with serologic resolution of infection (with loss of HBsAg, undetectable serum HBV DNA, and appearance of anti-HBs) HBV ccc DNA can remain in hepatocytes and other patients cells for life[16]. There are several risk factors for reactivation of HBV infection while undergoing IS therapy, most of them were researched in patients undergoing chemotherapy[17-20]. The most common risk factors are host factors, underlying disease, type of IS therapy received and baseline HBV status[21]. According to the research done by Yeo W et al. out of 78 HBsAg positive patients 29 % of male patients had reactivation of HBV infection as opposed to just 10 % of female patients[20]. Viral factors are another important factor in HBV reactivation. Chronically infected patients with positive HBsAg have a higher risk of reactivation compared with anti-HBc-positive patients who

are HBsAg-negative. In HBsAg-positive patients, the levels of HBV DNA prior to therapy are associated with risk of reactivation, with those having relatively high levels (> 2000 IU) being at higher risk compared with those having lower levels of HBV DNA[22]. In patients who are HBsAg-negative and anti-HBc-positive, anti-HBs level is thought to be an important factor as well, with those having undetectable anti-HBs level at the onset of IS therapy and those who have loss of anti-HBs during IS therapy being at increased risk for reactivation[23]. This could be one of the reasons why there wasn't a reactivation in our patient since he retained his anti-HBs levels constant throughout his IS therapy. Nevertheless, we could also presume that he did not have HBV cccDNA in his hepatocytes. Since our patient received kidney transplant and was put on IS therapy, it might have been presumed that his HBV infection would have reactivated if he had had the virus silently hidden in hepatocytes, especially considering the type of his IS therapy, which consisted of a glucocorticoid (prednisone), calcineurin inhibitor (CsA) and inhibitor of inosine-5'-monophosphate dehydrogenase (prodrug mycophenolate mofetil)[24]. Corticosteroids are the most longstanding and hence most commonly used of the immunosuppressants. In addition to their effect on T-cell function, corticosteroids directly enhance HBV replication through the interaction with the HBV glucocorticoid responsive element (a transcriptional regulatory element)[25-26]. Although steroids are administered at a range of dosages and durations for a variety of indications, it has been observed that a 4-week course of prednisone in a dosage higher than 20 mg has been associated with high risk (> 10 %) of HBV reactivation in the post-withdrawal (immune reconstitution) phase and worsened liver histology[26-27]. Our patient was on the constant IS therapy with prednisone (dosage of 30 mg per day and more for more than initial month after TX and 5 mg daily from the sixth month after TX and ongoing), from 2008 until 2017, during a span of 9 years, and HBV reactivation has not occurred yet. A new research done by Watashi K et al. has shown that CsA has a distinct effect on HBV[28]. CsA is known to have three major cellular targets: cellular cyclophilins, calcineurin and transporters, including the multidrug resistance (MDR) and MDR-related protein families[29-30]. In his research he discovered that CsA has reduced the infection of HBV[28]. It was previously reported that CsA suppressed HBV replication in a cell culture system carrying an HBV transgene[31]. Unfortunately it is still unclear whether clinically relevant doses of CsA could be helpful in preventing HBV reactivation after liver TX, and it also remains unknown in general whether entry inhibitors, a novel class of antivirals for viral control and cure of HBV that mostly targets HBV receptor and membrane transporter Sodium Taurocholate Cotransporting Polypeptide (such as CsA) could be effective in eliminating chronic HBV infection[28].

CONCLUSION

It has still remained unclear how spontaneous HBsAg seroconversion did happen in our patient after a long lasting infection. It is also unusual that 11 years after seroconversion his HBV markers are still unchanged (HBsAg negativity) and show signs of a resolved HBV infection, even though he was immunosuppressed due to kidney TX for already 9 years. It is possible that his anti-HBs levels are high enough to protect him and inhibit HBV reactivation, or the virus has not been dormant in his hepatic cells at all. Finally, there could have been a protection by CsA, but there isn't enough scientific evidence for its role in HBV reactivation.

Conflicts of interest statement: the authors report no conflicts of interest.

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