

Seroconversion of HBsAG coincides with hepatitis A super-infection: A case report

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Abstract

BACKGROUND

Hepatitis B virus (HBV) is a hepatotropic virus that can cause acute and chronic liver damage. According to the world health organization 257 million people are infected with chronic HBV infection worldwide. Super-infection with other hepadnaviruses, including hepatitis A virus (HAV), hepatitis C virus, hepatitis D virus, and hepatitis E virus is associated with increased risk of acute liver failure in patients with chronic HBV.

CASE SUMMARY

Here, we report a case of a 47-year old male patient with HBV-related compensated Child A cirrhosis, who presented with general fatigue, malaise and laboratory signs of acute hepatitis. Although the patient was regularly seen at a specialized university liver unit, the HAV vaccination status was unclear. Acute HAV super-infection was diagnosed by positive serological and polymerase chain reaction analysis. Following acute HAV super-infection, spontaneous HBsAg elimination and development of an anti-HBs titer were observed.

CONCLUSION

This case illustrates the importance of carefully checking the vaccination status. In our patient, unspecific immunological responses to HAV led to functional cure of HBV.

Key words: Chronic hepatitis B infection; Liver cirrhosis; Acute hepatitis A infection; HBsAg clearance; Functional cure; Case report

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Core tip: In patients with chronic hepatitis B virus (HBV) infection, super-infection with other hepatotropic viruses can lead severe liver diseases with acute on chronic liver failure, underlying the need to check for a complete hepatitis A virus (HAV) vaccination status. Here, we present an unvaccinated patient with HBV related liver cirrhosis who experienced an acute HAV super-infection. HAV infection was spontaneously cleared without signs of acute liver failure. Furthermore, most likely to an unspecific immunological response functional cure of HBV was observed (seroconversion of HBsAg to anti-HBs).

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INTRODUCTION

HBV infection and its consequences are a major global health problem. Approximately 4.7 million new cases of chronic hepatitis B infection were reported in 2015^[1]. Chronic hepatitis B virus (HBV) infection kills more than 1 million persons each year by causing cirrhosis, hepatocellular cancer, or both. This accounts for as many global deaths as those due to human immunodeficiency virus (HIV) infection, tuberculosis, or malaria^[2].

Super-infection with other hepatotropic viruses, including hepatitis A virus (HAV), hepatitis C virus (HCV), hepatitis D virus (HDV), and hepatitis E virus (HEV) can lead more severe disease course and has a higher risk of acute liver failure in patients with chronic HBV infection, especially in cirrhotic patients^[3-5]. Vaccination is aimed at preventing HAV super-infection in patients with chronic liver diseases^[6].

In patients with chronic HBV infection, the most desirable endpoint and a proposed definition of functional cure is clearance of hepatitis B surface antigen (HBsAg) from serum, so called occult HBV according to the EASL HBV guideline^[7].

Treatment-related HBsAg loss and seroconversion to anti-HBs rarely occurs and more often after interferon treatment than in patients treated with nucleotide analogue (NA) treatment^[8,9]. Here, we report a unique case of functional cure after super-infection with HAV in a patient with HBV-related liver cirrhosis in whom HAV-vaccination was missed.

CASE PRESENTATION

Chief complaints

In November 2018, a 47-year old Caucasian male patient consulted his family physician due to complaints of an acute gastro-intestinal infection. Symptoms included nausea, vomiting and abdominal cramps for the past two days. The patient was sent home with no specific treatment. Four days later, the patient's condition worsened and he presented with a mild scleral icterus.

History of past illness

The patient was known to be HBsAg and HBeAg positive since 2015 (Table 1). Based on transient elastography measurements (Fibroscan® 47 kPa), compatible ultrasound findings and laboratory results, he was diagnosed with compensated liver cirrhosis (Child-Turcotte-Pugh A). After the initial diagnosis in 2015, the patient was treated with tenofovir disoproxil fumarate (TDF) (245 mg once daily) with good treatment adherence and response. Under NA treatment, HBeAg seroconversion occurred after two years and HBsAg continuously decreased (Table 1).

The patient was tested negative for hepatitis C, D and/or HIV-1/2 co-infection. Further vaccination including HAV status of the patient was unclear. Erroneously, serological testing for hepatitis A virus was neither performed nor documented.

Personal and family history

Apart from HBV related liver cirrhosis the patient had no notable personal or family history.

Table 1 Clinical course of chronic hepatitis B virus infection

	September 2015	May 2016	June 2017	November 2018	June 2019	September 2019
	Start of NUC-therapy			Acute HAV-superinfection	Clearance of HBs antigen	Clearance of HBs antigen
HBs-antigen QL	Positive	Low	Low	Low	Negative	Negative
HBs antigen (IU/mL)	1 986.0	1 956.0	64.12	0.04	0.00	0.00
anti-HBs QL	Negative	Negative	Negative	Negative	Positive	Positive
anti-HBs (IU/mL)	Negative	Negative	Negative	Negative	159.21	380.29
anti-HBc IgM QL	Positive	Negative	Negative	Negative	Negative	Negative
HBe-antigen QL	Positive	Positive	Negative	Negative	Negative	Negative
anti-HBe	4371.0	2.94	1.37	Negative	Negative	Negative
HBV-PCR QL	Positive	Low	Low	Positive	Negative	Negative
HBV-PCR (IU/mL)	380000	20	150	< 10	BDL	BDL
GOT (U/L)	78	25	19	1334	14	13
GPT (U/L)	148	40	25	3387	20	20

Glutamic oxalacetic transaminase and glutamate pyruvate transaminase (Reference: 10-50 U/L). BDL: Below detection limit; HAV: Hepatitis A virus; GOT: Glutamic oxalacetic transaminase; GPT: Glutamate pyruvate transaminase; HBs: Hepatitis B surface; HBV: Hepatitis B virus; IgM: Immunoglobulin M; PCR: Polymerase chain reaction.

Physical examination upon admission

On admission, the patient presented slightly jaundiced, he was alert and fully oriented although he reported to be fatigued. He did not have any associated rash, fever or night sweats. He denied alcohol consumption, intravenous drug abuse or unprotected sexual intercourse.

Laboratory examinations

Initially, laboratory findings were all within the normal range (hemoglobin: 15.1 g/dL; leucocytes: 3.9 Mrd/L; aspartate aminotransferase: 38 U/L; alanine aminotransferase: 48 U/L; glutamyl transpeptidase: 41 U/L).

At time of admission, liver enzymes were dramatically elevated indicating an acute hepatitis (aspartate aminotransferase: 3542 U/L; alanine aminotransferase: 4857 U/L; glutamyl transpeptidase: 231 U/L; bilirubin: 5 mg/dL, albumin: 33.6 g/L; thrombocytes: 226 Mrd/L).

Imaging examinations

Liver ultrasound demonstrated no indication for mass or vascular problem as cause for the ALT elevation.

Further diagnostic work-up

Serological testing indicated an acute infection with HAV (HAV IgM QL positive, HAV IgG/IgM QL positive, HAV IgM > 7.00). Polymerase chain reaction for HAV detected viral particles in blood and stool samples (CT 29).

Tests for HCV, HDV and HEV were consistently negative. There was no evidence of acute exacerbation of his chronic HBV infection (Table 1). Without any specific treatment, liver enzymes promptly decreased and normalized within thirty days after infection. Hepatic function and synthesis was not impaired. The patient was discharged in improved clinical condition two days after admission.

Six months after HAV super-infection the patient presented for a follow-up visit at our outpatient clinic for viral hepatitis. A spontaneous HBs-Ag elimination occurred and a strong anti-HBs titer of 159.21 IU/mL was measured. Treatment with TDF was continued for three more months.

FINAL DIAGNOSIS

Acute HAV super-infection in a patient with HBV-related liver cirrhosis.

TREATMENT

No specific treatment was initiated.

OUTCOME AND FOLLOW-UP

HAV super-infection was cleared spontaneously. Furthermore, unspecific immunological responses to acute HAV super-infection led to functional cure of chronic HBV infection.

DISCUSSION

Patients with chronic liver diseases have a considerably higher morbidity and mortality from superimposed hepatitis, such as acute HAV infection^[10]. The Centers for Disease Control and Prevention published recommendations concerning HAV vaccination for disease prevention in patients with chronic liver diseases^[6]. Here, we report about a patient with HBV-related liver cirrhosis who was diagnosed with HAV super-infection. Despite regular follow-up visits at our specialized outpatient clinic for viral hepatitis, his vaccination history was not documented. The patient did not develop acute on chronic liver failure following HAV-super-infection and liver enzymes normalized promptly.

Our case emphasizes the responsibility of physicians to regularly screen and update the immunization status of their patients. Vaccinations must be renewed appropriately, specifically in immunocompromised patients.

The optimal end point of HBV treatment that is aimed for, is the loss of HBsAg and anti-HBs seroconversion. Unfortunately, these goals are rarely achieved with current drug therapeutical options. Many additional criteria influence the chance for HBsAg seroconversion such as host genetic, immunological, and viral factors, *e.g.* spontaneous mutations in cirrhosis patients. However, the mechanism of functional cure, and especially the underlying immune mechanisms, remain ill-understood^[11].

HBsAg elimination due to acute super-infection with other hepatotropic viruses has only rarely described in the literature. To the opposite, the majority of cases with HDV super-infection result in severe and progressive liver disease. Only a small number of patients are reported to clear HBsAg with permanent clearance of HBV and HDV infection^[12,13]. To our knowledge, HBsAg clearance following acute HCV super-infection has only been described in one single case so far^[14].

In our patient, treatment with TDF was started in 2015 and showed a good treatment response. HBe-Ag seroconversion was observed within two years, HBV viral load and HBsAg gradually decreased. Six months after HAV super-infection HBs-Ag clearance was detectable and the patient developed a robust anti-HBs titer (Table 1).

In HBeAg positive patients, HBsAg clearance and thus functional cure is described to only occur in about 1% of cases during antiviral treatment^[15]. Even though treatment-associated functional cure of HBV infection cannot be excluded in the present case, we postulate that HAV-associated hepatitis induced a nonspecific immunological response^[11]. For example, in case of acute hepatitis high amounts of Interferon- γ and tumor necrosis factor- α lead to lysis of infected hepatocytes. Interferon- γ and tumor necrosis factor- α are also known to suppress HBV replication and may have facilitated HBsAg clearance and may have helped to generate a robust anti-HBs titer in this case^[16,17].

CONCLUSION

In conclusion, the case reported here demonstrates that acute HAV super-infection may trigger sustained clearance of HBs-Ag in patients with chronic HBV infection. However, the case also underlines the critical importance of regular reviews of the vaccination status of our patients. Immunizations must be completed and renewed thoroughly, when available.

REFERENCES

- 1 **Thomas DL.** Global Elimination of Chronic Hepatitis. *N Engl J Med* 2019; **380**: 2041-2050 [PMID: 31116920 DOI: 10.1056/NEJMr1810477]
- 2 **Stanaway JD, Flaxman AD, Naghavi M, Fitzmaurice C, Vos T, Abubakar I, Abu-Raddad LJ, Assadi R, Bhala N, Cowie B, Forouzanfour MH, Groeger J, Hanafiah KM, Jacobsen KH, James SL, MacLachlan J, Malekzadeh R, Martin NK, Mokdad AA, Mokdad AH, Murray CJL, Plass D, Rana S, Rein DB, Richardus JH, Sanabria J, Saylan M, Shahraz S, So S, Vlassov VV, Weiderpass E, Wiersma ST, Younis M, Yu C, El Sayed Zaki M, Cooke GS.** The global burden of viral hepatitis from 1990 to 2013: findings from the Global Burden of Disease Study 2013. *Lancet* 2016; **388**: 1081-1088 [PMID: 27394647 DOI:]

- 10.1016/S0140-6736(16)30579-7]
- 3 **Fu J**, Guo D, Gao D, Huang W, Li Z, Jia B. Clinical analysis of patients suffering from chronic hepatitis B superinfected with other hepadnaviruses. *J Med Virol* 2016; **88**: 1003-1009 [PMID: 26509653 DOI: 10.1002/jmv.24417]
 - 4 **Cheng SH**, Mai L, Zhu FQ, Pan XF, Sun HX, Cao H, Shu X, Ke WM, Li G, Xu QH. Influence of chronic HBV infection on superimposed acute hepatitis E. *World J Gastroenterol* 2013; **19**: 5904-5909 [PMID: 24124337 DOI: 10.3748/wjg.v19.i35.5904]
 - 5 **Mori N**, Suzuki F, Kawamura Y, Sezaki H, Hosaka T, Akuta N, Kobayashi M, Saito S, Suzuki Y, Arase Y, Ikeda K, Kobayashi M, Kumada H. Determinants of the clinical outcome of patients with severe acute exacerbation of chronic hepatitis B virus infection. *J Gastroenterol* 2012; **47**: 1022-1029 [PMID: 22370817 DOI: 10.1007/s00535-012-0561-8]
 - 6 **Advisory Committee on Immunization Practices (ACIP)**. Fiore AE, Wasley A, Bell BP. Prevention of hepatitis A through active or passive immunization: recommendations of the Advisory Committee on Immunization Practices (ACIP). *MMWR Recomm Rep* 2006; **55**: 1-23 [PMID: 16708058]
 - 7 **European Association for the Study of the Liver**. EASL 2017 Clinical Practice Guidelines on the management of hepatitis B virus infection. *Journal of Hepatology* 2017; **67**: 370-398
 - 8 **Alawad AS**, Auh S, Suarez D, Ghany MG. Durability of Spontaneous and Treatment-Related Loss of Hepatitis B s Antigen. *Clin Gastroenterol Hepatol* 2020; **18**: 700-709.e3 [PMID: 31323381 DOI: 10.1016/j.cgh.2019.07.018]
 - 9 **Zhou K**, Contag C, Whitaker E, Terrault N. Spontaneous loss of surface antigen among adults living with chronic hepatitis B virus infection: a systematic review and pooled meta-analyses. *Lancet Gastroenterol Hepatol* 2019; **4**: 227-238 [PMID: 30679109 DOI: 10.1016/S2468-1253(18)30308-X]
 - 10 **Vento S**, Garofano T, Renzini C, Cainelli F, Casali F, Ghironzi G, Ferraro T, Concia E. Fulminant hepatitis associated with hepatitis A virus superinfection in patients with chronic hepatitis C. *N Engl J Med* 1998; **338**: 286-290 [PMID: 9445408 DOI: 10.1056/NEJM199801293380503]
 - 11 **Yuan T**, Jiang Y, Li M, Li W. Chronic hepatitis B surface antigen seroclearance-related immune factors. *Hepatol Res* 2017; **47**: 49-59 [PMID: 27084584 DOI: 10.1111/hepr.12726]
 - 12 **Chin KP**, Govindarajan S, Redeker AG. Permanent HBsAg clearance in chronic hepatitis B viral infection following acute delta superinfection. *Dig Dis Sci* 1988; **33**: 851-856 [PMID: 3378478 DOI: 10.1007/bf01550975]
 - 13 **Pastore G**, Monno L, Santantonio T, Angarano G, Milella M, Giannelli A, Fiore JR. Hepatitis B virus clearance from serum and liver after acute hepatitis delta virus superinfection in chronic HBsAg carriers. *J Med Virol* 1990; **31**: 284-290 [PMID: 2269880 DOI: 10.1002/jmv.1890310408]
 - 14 **Liaw YF**, Lin SM, Sheen IS, Chu CM. Acute hepatitis C virus superinfection followed by spontaneous HBeAg seroconversion and HBsAg elimination. *Infection* 1991; **19**: 250-251 [PMID: 1917039 DOI: 10.1007/bf01644957]
 - 15 **Lok AS**, Sulkowski MS, Kort JJ, Willner I, Reddy KR, Shiffman ML, Hassan MA, Pearlman BL, Hineostrota F, Jacobson IM, Morelli G, Peter JA, Vainorius M, Michael LC, Fried MW, Wang GP, Lu W, Larsen L, Nelson DR. Efficacy of Glecaprevir and Pibrentasvir in Patients With Genotype 1 Hepatitis C Virus Infection With Treatment Failure After NS5A Inhibitor Plus Sofosbuvir Therapy. *Gastroenterology* 2019; **157**: 1506-1517.e1 [PMID: 31401140 DOI: 10.1053/j.gastro.2019.08.008]
 - 16 **Tan A**, Koh S, Bertolotti A. Immune Response in Hepatitis B Virus Infection. *Cold Spring Harb Perspect Med* 2015; **5**: a021428 [PMID: 26134480 DOI: 10.1101/cshperspect.a021428]
 - 17 **Walker CM**. Adaptive Immune Responses in Hepatitis A Virus and Hepatitis E Virus Infections. *Cold Spring Harb Perspect Med* 2019; **9** [PMID: 29844218 DOI: 10.1101/cshperspect.a033472]



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