Analysis of Unusual Patterns of HBV Serologic Markers Including HBsAg, anti-HBc and anti-HBs

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The Master's Thesis
submitted to the Department of Medicine,
the Graduate School of Yonsei University
in partial fulfillment of the requirements for the degree
of Master of Medical Science

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December 2013

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December 2013

ACKNOWLEDGEMENTS

My most sincere acknowledgement goes out to professors, Hyon-Suk Kim, Jeon Han Park and Sang Hoon Ahn for their guidance of this work.

I also would like to appreciate professors and my co-workers in the Department of Laboratory Medicine for helping me. Last but not least, I am deeply indebted to my family, friends and my wife for all their support.

<TABLE OF CONTENTS>

LIST OF FIGURES

LIST OF TABLES

ABSTRACT

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Clinical significance of various patterns generated by serologic markers including HBsAg, anti-HBc and anti-HBs is well known. However, some unusual serologic patterns including “anti-HBc alone” and “coexistence of HBsAg and anti-HBs” are difficult to interpret. In this study, patients with “anti-HBc alone” and those with “coexistence of HBsAg and anti-HBs” were categorized and analyzed to evaluate the infection status of patients with unusual serologic patterns.

During the 7 years from January 2006 to December 2012, the hepatitis B screening results including concurrent HBsAg, anti-HBc and anti-HBs in Severance Hospital, Yonsei University College of Medicine were reviewed. Among 132,238 patients, “anti-HBc alone” was identified in 10,864 (8.2%) patients and “coexistence of HBsAg and anti-HBs” in 385 (0.3%) patients.

Patients with “anti-HBc alone” were classified into 4 categories as follows: 1) patients with past resolved HBV infection with decreased titers of anti-HBs, 1,087/10,864 (10.0%) cases, 2) patients with the ‘‘window period’’ of acute HBV infection, 20/10,864 (0.2%) cases, 3) patients with occult HBV infection with undetectable HBsAg, 406/10,864 (3.7%) cases, and 4) remaining patients unable to categorized, 9,351/10,864 (86.1%) cases.

Among 385 patients with “coexistence of HBsAg and anti-HBs”, 23 (6.0%) showed HBsAg disappearance and among those, 19 (4.9%) had seroconversed to anti-HBs positive on follow-up assays.

In summary, patients with unusual serologic patterns of HBV markers including “anti-HBc alone” and “coexistence of HBsAg and anti-HBs” were 8.2% and 0.3% of the total requested cases, respectively by current sensitive chemiluminiscent immunoassay. Among cases with “anti-HBc alone”, cases with past resolved HBV infection with decreased titers of anti-HBs were the most frequent (1,087/1,513; 71.8%) with the exception of unclassifiable patients. Within patients with “coexistence of HBsAg and anti-HBs”, positive results of HBsAg were continued in most individuals (111/134; 82.8%) who had follow-up results of HBsAg beyond 6 months from the day with coexistence pattern appeared.

Key words: anti-HBc alone; coexistence (concurrent) of HBsAg and anti-HBs; HBsAg; anti-HBc; anti-HBs; chemiluminescent immunoassay

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I. INTRODUCTION

Hepatitis B virus (HBV) is a major threat to global public health and more than 350 million people worldwide are chronic carriers of HBV[1]. In Korea, the prevalence of hepatitis B surface antigen (HBsAg) positive has recently been reported to be approximately 3.7% of the healthy population[2]. Serologic assays are essential to evaluate HBV infection, which accompanies characteristic changes in serum levels of serologic markers. The patterns of these markers are utilized to define different clinical status. The clinical significance of various patterns generated by serologic markers is well known. Assays including HBsAg, antibody to surface antigen (anti-HBs) and antibody to core antigen (anti-HBc)

are widely used for patients with HBV infection as initial and follow-up assessments. HBsAg is the serologic hallmark of HBV infection, which is detectable in serum between 4 to 10 weeks in acute infection. Chronic hepatitis B (CHB) is defined by persistence of HBsAg for more than six months[3]. Anti-HBs is a protective antibody generated after the resolution of HBV infection or vaccination. The appearance of anti-HBc indicates current or past HBV exposure and is usually detected throughout the course of HBV infection. Recently, the sensitivity and specificity of new immunoassays have been improved. However, unusual patterns of HBV markers are challenging to interpret and the clinical significance related to HBV infection is often complicated to define. Thus, this study was aimed to review the patients with "anti-HBc alone" and "coexistence of HBsAg and anti-HBs".

"Anti-HBc alone" is the serologic pattern of anti-HBc with the absence of both HBsAg and anti-HBs and is a relatively frequent finding in clinical laboratories[4, 5], although the clinical significance is not clearly revealed. Patients with "anti-HBc alone" can be categorized as the following: 1) "anti-HBc alone" caused by past resolved HBV infection with decreased titers of anti-HBs below the detection level over time[6], 2) the ''window period'' of acute HBV infection during the period after the disappearance of HBsAg and before the appearance of anti-HBs[7], 3) occult HBV infection with undetectable serum HBsAg[8], and 4) remaining cases unable to categorized.

"Coexistence of HBsAg and anti-HBs" is an infrequent serologic pattern and its actual status remains unknown. In many studies, the presence of both HBsAg and anti-HBs is reported to be highly associated with mutations of HBsAg,

especially, in the 'a' determinant[9, 10]. The 'a' determinant region of HBsAg is the major target of the antibody in active or passive immunization[9]. The titer of anti-HBs higher than 10 mIU/mL is considered to be protective against HBV infection[5]. The amino acid changes in HBsAg region may induce antibody escape and could cause active hepatitis even in the presence of anti-HBs[11].

In this study, the results of serologic markers of concurrent HBsAg, anti-HBc, and anti-HBs were analyzed in patients with unusual patterns of HBV serologic markers. Accumulated past and follow-up assays were reviewed during the years (January 2000 to April 2013).

II. MATERIALS AND METHODS

1. Subjects

From January 2006 to December 2012, serum samples of 176,814 from 132,238 patients were referred to screen HBsAg, anti-HBc, and anti-HBs simultaneously to Severance Hospital, Yonsei University College of Medicine. Among 132,238 patients, 120,989 (91.5%) showed typical serologic patterns. 11,249 (8.5%) individuals with unusual serologic patterns were subjected to this study. Total screening results were summarized in Table 1.

Table 1. Results of concurrent screening assays of HBsAg, anti-HBc and anti-HBs from 132,238 patients during the years 2006 to 2012 in Severance Hospital, Yonsei University College of Medicine

Serologic assays for HBV infection			Number of patients (%)		Interpretation
HBsAg	Anti-HBc	Anti-HBs			
Negative	Negative	Negative	27,313	(20.7)	No experience of exposure to HBV infection or vaccination Decline of antibody titer after vaccination
Negative	Negative	Positive	42,099	(31.8)	HBV immunity after vaccination
Negative	Positive	Positive	43,100	(32.6)	Resolved HBV infection
Positive	Positive	Negative	8,419	(6.4)	Acute / Chronic HBV infection Chronic HBV carrier state
Positive	Negative	Negative	58	(0.0)	Incubation period of acute HBV infection
Positive	Negative	Positive	3	(0.0)	Unusual serologic pattern - Coexistence of HBsAg and anti-HBs
Positive	Positive	Positive	382	(0.3)	
Negative	Positive	Negative	10,864	(8.2)	Unusual serologic pattern - anti-HBc alone
Total			132,238	(100.0)	

2. Serological assays of HBV markers

HBsAg, anti-HBc, anti-HBs, hepatitis B e antigen (HBeAg) and antibody to HBeAg (anti-HBe) were determined by chemiluminescent microparticle immunoassay using Architect i4000 SR (Abbott Diagnostics, Chicago, IL, USA). Chemiluminescent reaction measured with relative light units (RLU), and HBsAg, anti-HBc, HBeAg and anti-HBe were interpreted with the ratio of the sample to the cut-off (S/CO) RLU, where S/CO over 1.0 was considered positive, except anti-HBe (positive by S/CO below 1.0). The serum levels of anti-HBs were measured by Architect i4000 SR and concentration values exceeding 10 mIU/ml were considered as positive. Anti-HBc IgM was analyzed by VIDAS HBc IgM (Biomérieux, Marcy-l'Etoile, France) using enzyme linked fluorescence assay. Interpretation of HBc IgM was based on a Paul Erlich Institute (PEI) standard unit and cut-off values of PEI U/ml were as follows: below 5 was negative; over 10 was positive; between 5 and 10 was equivocal. All tests were carried out according to manufacturers' protocols.

Coinfection status of hepatitis C virus (HCV) was determined by anti-HCV tests. Anti-HCV was detected by electro-chemiluminescent immunoassay using the Cobas® e601 anti-HCV system (Roche Diagnostics, Mannheim, Germany).

3. Molecular assays

Until March 2011, HBV nucleic acids of serum were extracted using QIAamp MinElute Virus spin kit (Qiagen, Hilden, Germany) and extracted DNA was amplified and quantified in an ABI Prism 7000 sequence detection system (Applied Biosystems, Foster City, CA, USA). Serum HBV DNA copy numbers

were determined by using real-time PCR (Primer Design Ltd., Millbrook Technology Campus, Southampton, UK) and results were reported as positive or negative on the basis of cycle threshold. Digene Hybrid capture assay (Digene Diagnostics, Beltsville, MD, USA) was used for quantitation of HBV DNA, and sensitivity of this assay was 0.5 pg/mL.

After March 2011, HBV molecular test was performed by fully automated commercial real-time quantitative PCR system, COBAS AmpliPrep/COBAS TaqMan HBV test (Roche Diagnostics, Branchburg, NJ, USA).

4. Medical record analysis

During the years 2006 to 2012, the medical history of the patients with unusual HBV serologic patterns were reviewed. Furthermore, the accumulated past and follow-up data of those subjects were examined throughout an extended period from January 2000 to April 2013 to investigate the changes in serologic markers.

In patients with “coexistence of HBsAg and anti-HBs”, the progress of infection status was analyzed based on follow-up results of assays. The follow-up data was collected for a minimum of 6 months from the time of “coexistence of HBsAg and anti-HBs” to confirm the final infection status.

III. RESULTS

1. Patients with “anti-HBc alone”

Among 132,238 patients, 10,864 (8.2%) individuals demonstrated “anti-HBc alone”. The demographic characteristics of these 10,864 are summarized in Table 2. The mean age was 59.8 years (standard deviation 12.6, range 0–99), and the total population consisted of 6,818 males and 4,047 females. Immunosuppressants were administered in 1,209 patients and 449 patients demonstrated HCV co-infection.

HBV DNA assay tested within 7 days before or after the time of “anti-HBc alone” was considered to have been simultaneously tested with HBV serologic assays, and in 266 patients out of 132,238 patients, HBV DNA was tested simultaneously with “anti-HBc alone”. HBV DNA was detected in 18 patients and undetected in from 248 patients.

Patients with “anti-HBc alone” were classified into 4 categories including past resolved infection with acquired immunity, window period of acute hepatitis B, suspected occult HBV infection, and unclassified.

Flow diagram of patients with “anti-HBc” alone was demonstrated in Figure 1. Past results of HBV serologic tests were examined in all 10,864 patients, and 765 patients had positive results of anti-HBs before having “anti-HBc alone” pattern. Among the 765 patients, hepatitis B immune globulin (HBIG) was administered in 5 patients for treatment of liver transplantation and prevention of vertical transmission to neonate. In these 5 patients, antecedent positive result of anti-HBs was expected to be caused by the usage of HBIG. Past anti-HBs (+) prior to “anti-HBc alone” in 760 patients out of 10,864 was considered as active immunity after HBV exposure. In 10,099 patients without past results of anti-HBs (+), 401 had histories of chronic hepatitis B (CHB) and the other 9,698

had no history of CHB. In addition to 5 patients who had be administered HBIG before having “anti-HBc alone”, 401 patients with CHB history and HBV carriers were categorized as occult HBV infection group. In 9,698 patients without CHB history, 20 patients were classified as a group of ‘window period’ of acute hepatitis B. From the other 9,678, excluding group of ‘window period’ out of 9,698 people, 327 patients demonstrated anti-HBs (+) and HBsAg (-) on follow-up assays. The rise of serum anti-HBs was considered to be an anamnestic response to HBV exposure. These 327 cases were categorized as past resolved HBV infection with immunity in addition to the 760 patients with anti-HBs (+) before having “anti-HBc alone”. Remaining 9,351 patients could not be classified due to the lack of clinical data.

In summary, 1,087 patients were labeled as individuals with past HBV infection where anti-HBs have decreased below the detection level, 18 patients were considered as ‘window period’, and 406 patients were suspected of chronic infection with undetectable HBsAg. The other 9,351 patients were categorized as undetermined owing to insufficient data.

HBV DNA assay was performed simultaneously with “anti-HBc alone” in 266 patients, where the presence of HBV DNA was found in 19 patients (7.1%). Serum HBV DNA was detected in 2 out of 25 individuals with past resolved HBV infection, 2 out of 6 individuals with acute hepatitis B, 15 out of 102 individuals with occult CHB, and 0 out of 134 unclassified individuals.

In follow-up assays after the time of “anti-HBc alone”, serum HBsAg positive and/ or HBV DNA detection were found in 39 patients. These 39 patients consisted of 6 with past resolved infection, 27 with occult CHB and 6

unclassified.

Table 2. Demographic characteristics of 10,864 patients with "anti-HBc alone"

Characteristics	Number of patients with "anti-HBc alone"	%
Gender		
Male	6,818	62.8
Female	4,047	37.2
Age (mean±SD)	59.8 ± 12.6	
≤20	42	0.4
21 - 40	660	6.1
40 - 60	4,736	43.6
60 - 80	5,010	46.1
≥81	417	3.8
Administration of immunosuppressant	1,209	11.1
HCV coinfection	449	4.1

Abbreviations: SD, Standard Deviation

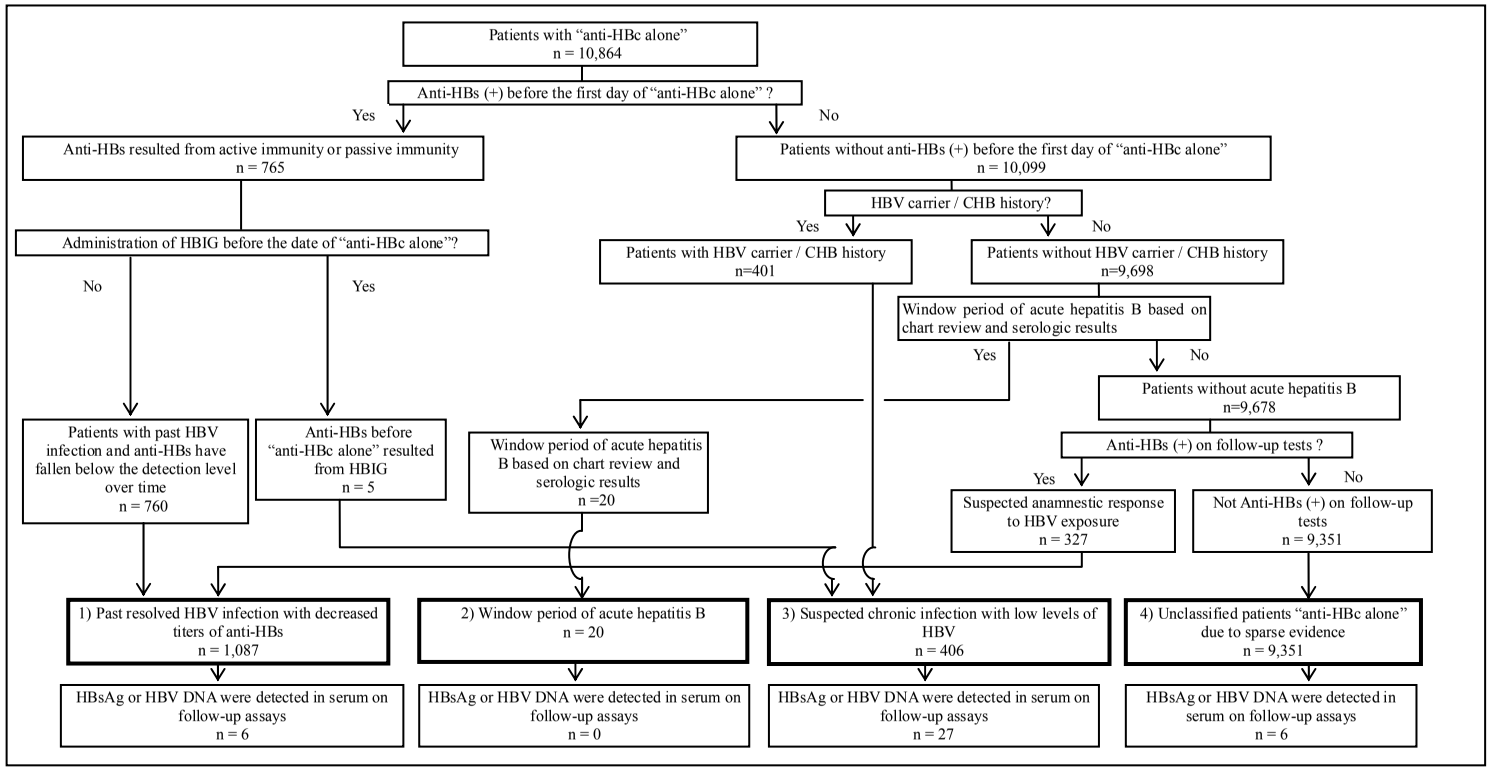

Figure 1. Classification of patients with "anti-HBc alone" according to medical chart review and follow-up results of HBsAg and HBV-DNA.

2. Patients with “coexistence of HBsAg and anti-HBs”

Among 132,238 patients referred with concurrent HBsAg, anti-HBc, and anti-HBs, the pattern of “coexistence of HBsAg and anti-HBs” was demonstrated in 385 (0.3%) patients. The demographic characteristics of these 385 are summarized in Table 3. The mean age was 51.1 years (standard deviation 14.6, range 0-89), consisting of 234 males and 141 females. Immunosuppressants were administered in 71 patients due to organ transplantation and other causes including autoimmune diseases. Anti-neoplastic agents were administered in 117 patients.

From the follow-up serologic HBV assays of the total of 385 patients, 111 patients presented positive HBsAg [HBsAg/anti-HBs (+/+), n=45; HBsAg/anti-HBs (+/-), n=44; HBsAg/anti-HBs (+/not tested), n=22] and 23 demonstrated negative HBsAg [HBsAg/anti-HBs (-/+), n=19; HBsAg/anti-HBs (-/-), n=3; HBsAg/anti-HBs (-/not tested), n=1]. The remaining 251 patients had no follow-up results beyond 6 months. Follow-up serologic HBV results in patients with “coexistence of HBsAg and anti-HBs” are demonstrated in Figure 2.

Among 385 patients with “coexistence of HBsAg and anti-HBs”, 296 were HBV carriers or had a history of CHB. The remaining 89 patients had no history related to HBV infection. The 296 patients with CHB history classified according to anti-viral treatment are demonstrated in Figure 3. Nucleos(t)ide analogues for HBV infection were administered in 111 out of 296 patients after the period of “coexistence of HBsAg and anti-HBs”. Among these 111 patients, HBsAg positive at final follow-up assay was presented in 46 patients, and 9 patients had HBsAg negative at final assay in response to anti-viral therapy. Among 296 patients with

CHB, HBsAg (+) on follow-up assays were noted in 103 patients [HBsAg/anti-HBs (+/+), n=39; HBsAg/anti-HBs (+/-), n=42; HBsAg/anti-HBs (+/not tested), n=22] and HBsAg (-) on final follow-up assay was presented in 16 patients [HBsAg/anti-HBs (-/+), n= 14; HBsAg/anti-HBs (-/-), n=1; HBsAg/anti-HBs (-/not tested), n=1].

Among 89 patients without CHB history, 6 were assumed as acute hepatitis B with ALT elevation in relation to clinical records. In 83 patients without history of hepatitis B, 12 patients had follow-up results. HBsAg (+) on later assay was demonstrated in 7 patients [HBsAg/anti-HBs (+/+), n=5; HBsAg/anti-HBs (+/-), n=2] and HBsAg (-) on later assay was presented in 5 patients [HBsAg/anti-HBs (-/+), n= 4; HBsAg/anti-HBs (-/-), n=1] among 83 patients without history of hepatitis B. In 6 patients with acute hepatitis B, disappearance of HBsAg was noted in 4 patients after conservative care (n=2) and anti-viral treatment (n=2), and within 6 months in 2 patients with acute hepatitis. HBV DNA was detected from 1 patient after 1 year, which suggested a progression to chronic hepatitis B. The remaining 1 patient with acute hepatitis B had no follow-up result.

Thirteen patients experienced disappearance of HBsAg without nucleos(t)ide analogue treatment, and among these patients, seroconversion to anti-HBs was noted in 11 patients.

Table 3. Demographic characteristics of 385 patients with "coexistence of HBsAg and anti-HBs" pattern

Characteristics	Number of patients with "coexistence of HBsAg and anti-HBs"	%
Gender		
Male	234	60.8
Female	151	39.2
Age (mean±SD)	51.1 ± 14.6	
≤20	10	2.6
21 - 40	65	16.9
41 - 60	220	57.1
61 - 80	84	21.8
≥81	6	1.6
HBV carrier / CHB history	296	76.9
Anti-neoplastic agents	117	30.4
Immunosuppressant administration	71	18.4
Organ transplantation	43	11.2
Other	28	7.3

Abbreviations: SD, Standard Deviation;

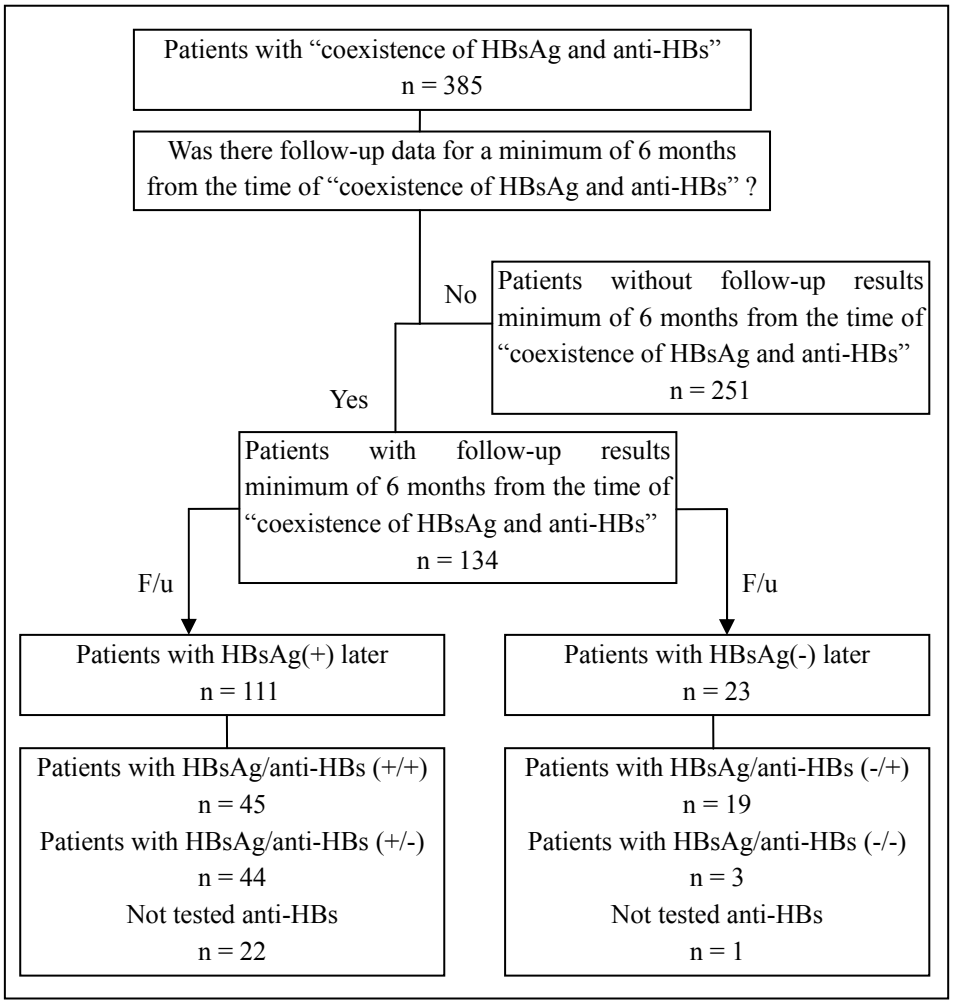

Figure 2. Follow-up results of HBsAg and anti-HBs in patients with "coexistence of HBsAg and anti-HBs".

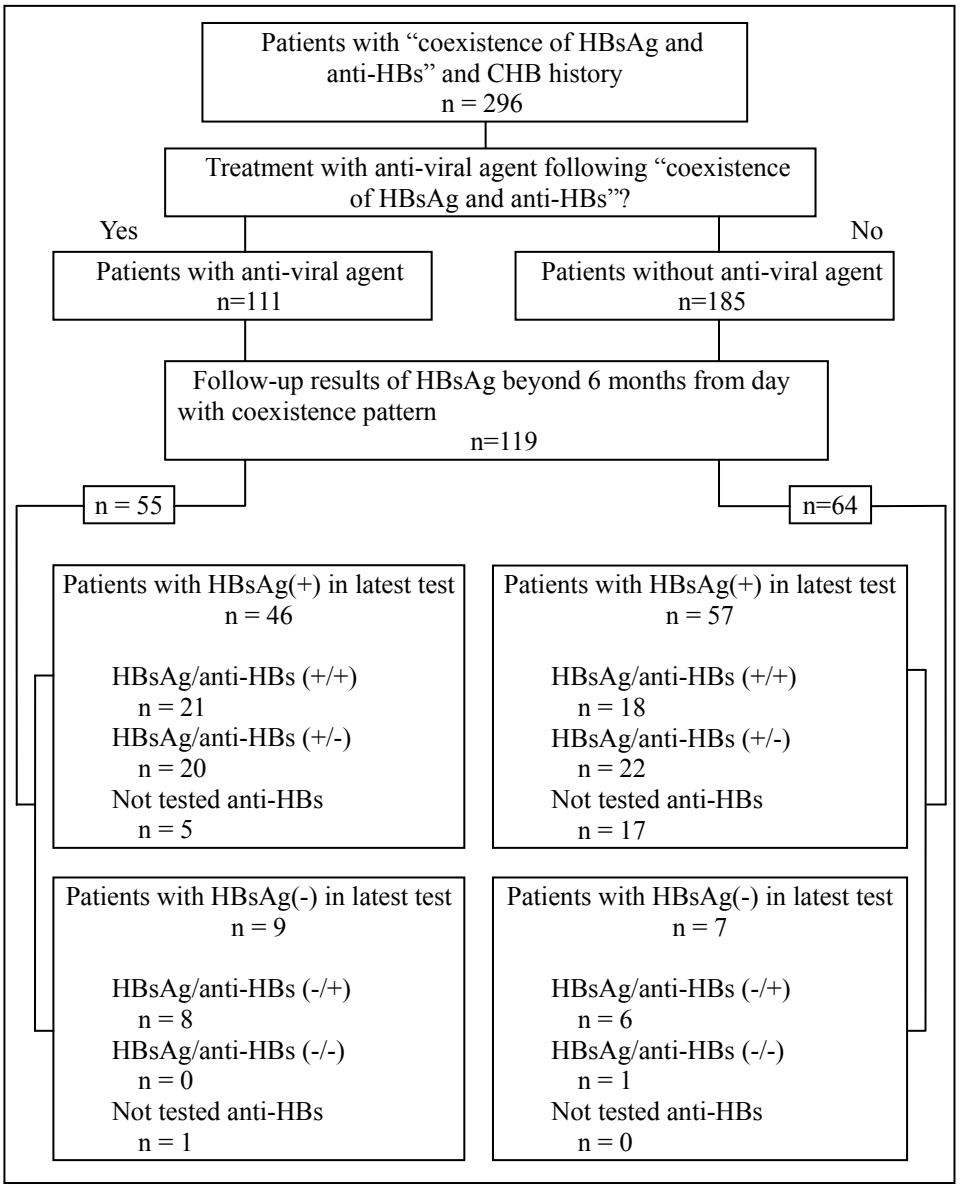

Figure 3. Follow-up results according to anti-viral treatment in 296 patients with CHB history out of 385 individuals with "coexistence of HBsAg and anti-HBs".

IV. DISCUSSION

The present study was aimed to review patients with “anti-HBc alone” and “coexistence of HBsAg and anti-HBs” to analyze unusual patterns of HBV markers that are clinically challenging to interpret.

In this study, the unusual serologic patterns of HBV markers consisted of approximately 8.5% of the total cases. “Anti-HBc alone” was noted in 10,864 (8.2%) patients and “coexistence of HBsAg and anti-HBs” in 385 (0.3%) patients among 132,238 patients (176,813 samples).

In the classification of patients with “anti-HBc alone”, most individuals (9,351 patients, 86.1%) were categorized to group 4, uncategorized patients, and when unclassified patients was excluded, cases with past resolved HBV infection with decreased titers of anti-HBs, group 1, were the most frequent (1,087 patients, 71.8%).

Among patients with “coexistence of HBsAg and anti-HBs”, a majority (82.8%) of patients continued to have HBsAg positive results and 45 patients (33.6%) had persistent state of “coexistence of HBsAg and anti-HBs” on follow-up among individuals who had follow-up data for a minimum of 6 months from the time of “coexistence of HBsAg and anti-HBs”.

The prevalence of “anti-HBc alone” may be dependent on study population. The pattern of “anti-HBc alone” tends to increase in high incidence of HBV prevalence. A study reported that the prevalence of ‘‘anti-HBc alone’’ was variable according to study groups as 1.8%, 10.2%, and 21.5% in asymptomatic outpatients, drug

users, and patients with hepatic cell carcinoma, respectively[4]. In another study from a Korean tertiary hospital with a similar population of interest to the present study, “anti-HBc alone” was detected in 8.9% in serum samples referred for routine examination of viral hepatitis[12]. This is similar to the results of the present study demonstrating an 8.2% prevalence of “anti-HBc alone”.

In patients with “anti-HBc alone” results, the HBV DNA assays were performed within 1 week before and after “anti-HBc alone” in 266 patients. These adjacent HBV DNA assays can be considered contemporary with “anti-HBc alone”. Serum HBV DNA was detected contemporarily in 2 patients categorized as ‘window period’ of acute hepatitis B, and 15 patients categorized as occult CHB. Detection of serum HBV DNA in patients with acute hepatitis B and CHB was predictable. However, Simultaneous HBV DNA positive and “anti-HBc alone” was found in 2 patients of group 1, past resolved HBV infection. These 2 were recovered from CHB and had anti-HBs positive before “anti-HBc alone”, and 1 patient had pancreatic cancer when “anti-HBc alone” was shown. Reactivation of HBV in patients with past resolved HBV infection has been reported in a few cases[13-16]. Serum HBV DNA positive in 2 patients could be interpreted as reactivation of HBV.

Mutations of HBsAg region, a major antibody binding site, could cause inability to detect HBsAg by commercial HBV immunologic assays[11], or could induce “coexistence of HBsAg and anti-HBs”[9, 11, 17]. The “a” dominant epitope within the major hydrophilic region of the S gene and mutations of this determinant has been widely reported[9-11]. Presence of HBV DNA in patients with “anti-HBc alone”

suggests infection of mutant HBV with undetectable HBsAg by chemiluminescent microparticle immunoassay.

In the present study, 6 patients among group 1, past resolved HBV infection, had HBsAg positive results on follow-up assays. These patients had medication histories of immunosuppressant and chemotherapy for the treatment of cancer. Reactivation of HBV in patients with anti-HBs positive results is rare but reported in a few studies[13-16]. Immune suppressed condition can be the risk factor for reactivation of infection[13, 16, 18].

Co-infection of HCV could suppress HBV replication and decrease titers of HBsAg leading to an "anti-HBc alone" state[6]. Among the total 10,864 patients with "anti-HBc alone", 449 had coinfection of hepatitis C and only 7 patients had HBsAg or HBV PCR positive results. It is possible that the remaining ~~other~~ 442 had occult HBV infection in serum suppressed by HCV coinfection.

It has been known that the category of past resolved HBV infection with decreased titers of anti-HBs is the most frequent among "anti-HBc alone" population[5, 19]. In the present study, past anti-HBs positive due to active immunity before "anti-HBc alone" was noted in 760 individuals, and anti-HBs positive on follow-up assays due to anamnestic immune response to HBV exposure after "anti-HBc alone" was demonstrated in 327 individuals[20]. The total of 1,087 cases categorized as a group of past resolved HBV infection with decreased titers of anti-HBs was the most frequent as 71.8%, 1,087 out of 1,513 individuals, with the exception of 9,351 unclassifiable patients. In another study, HBV vaccination was attempted to individual with "anti-HBc alone", and positive conversion of

anti-HBs occurred in 78.3% after one inoculation. Positive conversion of anti-HBs after vaccination could be interpreted as past acquired immunity and other patients with non conversion of anti-HBs could be suspected as occult infection. In this study, it is possible that a status of past resolved HBV infection with decreased anti-HBs titers was estimated to be the majority in 9,351 unclassifiable patients. The prevalence of anti-HBs coexistence with HBsAg was 4.3 % of HBsAg positive patients (385/8,862 individuals) in the present study population. In other studies, proportion of coexistence of both markers were reported as 3.1% in 495 individuals with HBsAg (+)[10], and 7.1% in 1,132 HBV carriers with HBsAg (+)[9]. The prevalence of "coexistence of HBsAg and anti-HBs" in the present study was similar to other studies.

HBV reactivation could occur in patients with immunocompromised status[18, 21], and it was reported that patients with both HBsAg and anti-HBs were predominantly immunosuppressed (69%)[10]. In the present study, 145 out of 385 patients (38.2%) with "coexistence of HBsAg and anti-HBs" and 141 out of 296 patient (47.6%) with CHB history had possible causes that could have reduced immunity including administration of immunosuppressants and anti-neoplastic agents.

Mutations in region of HBsAg could generate changes in anti-HBs binding site, then anti-HBs could not neutralize HBV and status of "coexistence of HBsAg and anti-HBs" could occur[9, 11, 17]. It is reasonable to assume that immune escape mutants can be detected in many patients with "coexistence of HBsAg and anti-HBs" in this study. However, nucleotide sequencing assay that could confirm

HBsAg mutations was not performed and this was a limitation of this study. HBIG was administrated in 35 patients with CHB, and “coexistence of HBsAg and anti-HBs” could result from the infection of a wild type HBV with passive immunity by HBIG administration in these patients.

In 385 patients with “coexistence of HBsAg and anti-HBs”, 273 had no anti-viral treatment, and among these 273 patients, 78 had follow-up results of HBsAg and anti-HBs. Among the 78 patients, disappearance of HBsAg occurred in 13 patients without anti-viral treatment. Serologic patterns and medical histories of these 13 individuals were reviewed by follow-up results. One patient with acute hepatitis B temporarily had both positive results of HBsAg and anti-HBs, and HBsAg negative and anti-HBs positive on follow-up assay meant spontaneous resolution of acute hepatitis B. In this patient with resolved acute hepatitis B, “coexistence of HBsAg and anti-HBs” could be interpreted as a natural course of acute infection. Among the other 12 patients, 8 patients passed through immunocompromised conditions such as progressed cancer, operation for cancer treatment, organ transplantation, transcatheter arterial chemoembolization, and administration of anti-neoplastic agents or steroid before HBsAg seroclearance. Considering the fact that reactivation of HBV can occur in immunocompromised status, the HBsAg seroclearance demonstrated in patients with adverse conditions was an unusual event. Spontaneous loss of HBsAg or false positive HBsAg could account for the status of these patients. Disappearance of HBsAg and seroconversion to anti-HBs in patients with CHB have rarely been reported and are usually associated with complete elimination of HBV[22]. Reduced affinity and

decreased ability to identify mutated HBsAg by anti-HBV antibodies used in HBV serological assays were reported, which could cause false negative HBsAg[11]. Two possibilities should be considered in the evaluation of unexplainable HBsAg disappearance in patients without anti-viral treatment.

V. CONCLUSION

In categorization of patients with “anti-HBc alone”, cases with past resolved HBV infection with decreased titers of anti-HBs were the most frequent (71.8%), when unclassified patients were excluded.

In patients with “coexistence of HBsAg and anti-HBs”, the majority (82.8%) continuously displayed positive results of HBsAg. 33.6% of the patients persistently demonstrated “coexistence of HBsAg and anti-HBs” among those who had follow-up results of HBsAg beyond 6 months from the day of appearance of a coexistent pattern.

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ABSTRACT(IN KOREAN)

비전형적 B형간염 바이러스 혈청표지자 검사 양상에 대한 분석

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B형 간염의 진단과 평가에서 혈청학적 표지자 검사는 매우 중요하다. 환자의 검사결과가 anti-HBc 단독양성이나 HBsAg 과 anti-HBs의 동시양성과 같은 비전형적 양상을 보일 경우 임상적 의미를 해석하기 어렵다. 본 연구에서는 비전형적 혈청학적 결과를 보인 환자들의 상태를 평가하기 위해 근래에 개선된 자동화된 B형간염 검사법의 도입 후 7년간 발생한 비전형적 결과를 총괄적으로 검토하였다. Anti-HBc 단독양성을 보인 환자들의 임상적 특징을 알아보고, 또한 HBsAg과 anti-HBs가 동시에 양성을 보인 환자들의 추적검사 결과를 확인해 보았다.

2006년부터 2012년까지 HBsAg, anti-HBc 그리고 anti-HBs 가 동시에 검사 의뢰된 환자는 132,238 명 (176,814 검체) 이었고, 이 중

anti-HBc 단독양성을 보인 환자는 10,864 명 (8.2%), HBsAg와 anti-HBs가 동시양성을 보인 환자는 385 명 (0.3%) 이었다. Anti-HBc 단독양성 환자들은 다음과 4가지 군으로 분류되었다. 1) 과거 HBV infection 후 획득한 anti-HBs 역가가 낮아진 환자 1,087 명 (10.0%), 2) 급성 B형 간염의 항체미형성기 (window period) 에 있는 환자 20 명 (0.2%), 3) 만성 B형 간염의 잠복감염으로 보이는 환자 406 명 (3.7%). 4) 정보부족으로 분류가 어려운 환자 9,351명 (86.1%).

HBsAg과 anti-HBs가 동시양성을 보인 환자 385 명 중 23 명에서 추후 검사상 HBsAg 음성 결과를 보였으며, 이중 19 명은 anti-HBs 양성 결과를 보였다.

본 연구에서 현재 사용하는 화학발광면역측정법 상 anti-HBc 단독양성이나, HBsAg 과 anti-HBs의 동시양성과 같은 비전형적 양상을 보인 환자들은 각각 8.2%, 0.3% 였다. Anti-HBc 단독양성 환자 분류에서 정보부족으로 분류가 어려운 환자를 제외했을 경우 과거 HBV infection 후 획득한 anti-HBs 역가가 낮아진 환자가 71.8% 로 가장 많았다. HBsAg과 anti-HBs가 동시양성을 보인 검사일 6개월 이후 추후 검사자료가 있는 환자들 중에서 지속적으로 HBsAg 양성을 보인 환자들이 82.8% 로 대다수를 차지하였다.

핵심되는 말: anti-HBc 단독양성; HBsAg, anti-HBs의 동시양성; B형 간염 바이러스 표면항원 (HBsAg); B형 간염 중심항체 (anti-HBc); B형 간염 표면항체(anti-HBs), 화학발광면역법