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ORIGINAL ARTICLE

Features of occult hepatitis B diagnostics in cancer patients

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ABSTRACT

Purpose of the study. Analysis of the frequency of detection of HBsAg-negative hepatitis B serological and molecular biological markers in cancer patients.

Materials and methods. The blood serum samples of patients hospitalized at the National Medical Research Centre for Oncology in 2016–2023 were studied. 41,523 samples were tested for HBsAg, 2,035 for anti-HBcore, of which 958 were tested simultaneously for both markers using the enzyme-linked immunosorbent assay (ELISA) or chemiluminescent immunoassay (CLIA). 1,380 samples were tested for the presence of hepatitis B virus (HBV) DNA in blood plasma using real time polymerase chain reaction (qPCR).

Results. The HBsAg prevalence in cancer patients accounted for 2.5 % (1051/41523), 23.7 % (483/2035) for anti-HBcore. Simultaneous examination for HBsAg and anti-HBcore revealed various combinations of markers. Among HBV-positive variants, the most common was the combination anti-HBcore+HBsAg-. The average number of such patients was 20.6 % (197/958). The simultaneous presence of both markers was noted in 4.6 % of patients (44/958). There were no isolated HBsAg detection cases. The total number of HBV+ individuals was 25.2 % (241/958). 81.7 % out of these (197/241) were HBsAg-negative. 219 samples with the HBV DNA presence in the blood plasma were identified. 19 of these were examined simultaneously for HBsAg, anti-HBcore. The majority (78.9 %) had all three markers. 21.1 % were HBsAg-negative but DNA-positive (latent form of infection), 15.8 % of which were anti-HBcore-positive, and 5.3 % did not have a single serological marker.

Conclusion. The detection of anti-HBcore in the absence of HBsAg can indicate the presence of occult forms of hepatitis B, which under conditions of drug immunosuppression can be reactivated. The identified significant percentage of cancer patients with occult hepatitis B variants highlights the necessity to expand the number of diagnostic markers for screening. Additional testing for anti-HBcore can significantly increase the likelihood of detecting HBV during prehospital testing.

Keywords: occult viral hepatitis B, HBV reactivation, oncological diseases

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Compliance with ethical standards: the ethical principles presented by the World Medical Association Declaration of Helsinki (1964, ed. 2013) were observed in the work. The study was approved by the Committee on Ethics at the Rostov Research Institute of Oncology (extract from the protocol of the meeting No. 30/1 dated 15/12/2015). Informed consent was obtained from every participant of the study

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ОРИГИНАЛЬНАЯ СТАТЬЯ

Особенности диагностики скрытой формы гепатита В у онкологических больных

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РЕЗЮМЕ

Цель исследования. Анализ частоты выявления серологических и молекулярно-биологических маркеров HBsAg-негативного гепатита В среди онкологических больных.

Материалы и методы. Исследовали сыворотки крови больных, госпитализированных в ФГБУ «Национальный медицинский исследовательский центр онкологии» Министерства здравоохранения Российской Федерации с 2016 по 2023 гг. Исследовано 41523 образца на HBsAg, 2035 – на суммарные анти-HBcore, из них 958 – одновременно на HBsAg и анти-HBcore методами иммуноферментного (ИФА) или иммунохемилюминесцентного анализа (ИХЛА), 1380 образцов – на наличие ДНК вируса гепатита В (ВГВ) в плазме крови методом полимеразной цепной реакции в режиме реального времени (ПЦР-РВ).

Результаты. Распространенность HBsAg среди онкологических больных составила 2,5 % (1051/41523), анти-HBcore – 23,7 % (483/2035). Одновременное обследование на HBsAg и анти-HBcore позволило выявить различные сочетания маркеров. Среди вариантов, положительных хотя бы по одному маркеру, самым распространенным оказался HBsAg-негативный, но анти-HBcore-позитивный. Количество таких больных в среднем составило 20,6 % (197/958). Одновременное присутствие обоих маркеров было отмечено в среднем у 4,6 % больных (44/958). Не было выявлено ни одного случая изолированного выявления HBsAg. Всего число лиц, инфицированных ВГВ, составило 25,2 % (241/958). Из них HBsAg-негативными оказались 81,7 % (197/241).

Было выявлено 219 образцов с наличием ДНК ВГВ в плазме крови. Из них 19 были обследованы одновременно на наличие HBsAg, анти-HBcore. У большинства (78,9 %) присутствовали все три маркера. HBsAg-негативными, но ДНК-позитивными были 21,1 % (скрытая форма инфекции), из них 15,8 % – анти-HBcore-позитивными, а 5,3 % не имели ни одного серологического маркера.

Заключение. Обнаружение антител к HBcoreAg при отсутствии HBsAg может свидетельствовать о наличии скрытой формы гепатита В, которая в условиях медикаментозной иммуносупрессии способна перейти в активную форму. Выявленный существенный процент онкологических больных со скрытым вариантом гепатита В подчеркивает необходимость расширения числа диагностических маркеров для скрининга. Дополнительное тестирование на анти-HBcore может существенно повысить вероятность выявления ВГВ на этапе догоспитального обследования.

Ключевые слова: скрытый вирусный гепатит В, реактивация ВГВ, онкологические заболевания

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INTRODUCTION

One of the most important problems of modern diagnosis of chronic hepatitis B is the ability of the pathogen to cause the so-called occult form of infection. The following synonyms are used in scientific publications to refer to it: "occult", "silent" and "latent", as well as different definitions are applied in accordance with various guidelines [1–3].

Therefore, according to the recommendations of the European Association for the Study of the Liver [1], "occult hepatitis B virus (HBV) infection" is simply the fifth and final phase of the development of chronic hepatitis B. This is the HBsAg-negative phase, which is characterized by serum negative HBsAg and positive antibodies to HBcAg (anti-HBc), with or without detectable antibodies to HBsAg (anti-HBs). Patients in this phase have normal ALT values and usually, but not always, undetectable serum HBV DNA. Hepatitis B virus DNA (in covalently closed form) is often found in the liver. It is emphasized that the absence of HBsAg can often be associated with the use of insufficiently sensitive methods for its detection. Thus, it is assumed that occult hepatitis B is either one of the outcome options for chronic HBV infection, or it is the result of a virus mutation that "eludes diagnosis", which, obviously, is not the same thing [3]. In the Chinese guidelines for the prevention and treatment of chronic hepatitis B, the occult form is mentioned as one of the types of clinical diagnosis with special characteristics (the surface antigen of the virus is not detected in blood serum, but its DNA can be detected in blood and/or liver tissue) [4]. The World Health Organization, as part of the annual meeting of the Asia-Pacific Association for the Study of the Liver (APASL), presented updated guidelines on hepatitis B, according to which the occult form is the fourth phase of chronic infection and is defined as the persistence of HBV DNA in the liver or blood serum in people in whom HBsAg is not detectable in the blood [5]. As for the Guidelines of the American Association for the Study of Liver Diseases (AASLD), in its latest edition, occult hepatitis B is mentioned only as a possible risk factor in organ transplantation [6].

Based on the results of two international seminars in Taormina devoted specifically to the issue of occult hepatitis B, in 2008 and 2019, the following definition of occult HBV infection was formulated [7, 8]. Occult HBV infection is defined as the presence of replication-competent HBV DNA (i. e. episomal covalently closed circular HBV DNA [cccDNA]) in the liver and/or HBV DNA in the blood of people with a negative test result for hepatitis B virus surface antigen (HBsAg) using currently available assays. Based on the profiles of HBV-specific antibodies, occult hepatitis B can be divided into the following types:

- serum positive: positive for anti-HBc and/or anti-HBs, the most common form of infection that accounts for about 78 % of cases. The serological profile of occult HBV infection may include anti-HBc (50 %), anti-HBs (35 %);
- serum negative: anti-HBc and anti-HBs negative [8].

The origin of the occult form of HBV infection is considered insufficiently studied. It is assumed that there are several possible mechanisms of its occurrence, including, first of all, pronounced suppression of viral replication and/or inhibition of S gene expression, mutations in the regulatory regions of the HBV genome, persistence of Ig-associated HBV immune complexes, viral interference, coincidence of the time of the study with the phase of the serological "window", integration of the viral DNA in the cellular genome, long-term persistence in the hepatocyte nucleus of cccDNA in the form of a stable episome, and others [9]. According to Semenov A. V. et al., the occult form of hepatitis B can be considered as the result of the implementation of various scenarios of interaction between the virus and the immune system, expressed in extremely diverse patterns in terms of the results of the determination of laboratory markers [10].

Since a fairly wide range of clinical conditions fall under the formal definition of "occult HBV infection" as the absence of HBsAg in the presence of DNA in serum or liver biopsy, it is not surprising that data on its prevalence in the world vary widely (from 1 to 87 %) and depend on the region, the method of determining the virus genome, the markers studied, and the diversity commercial kits for detecting HBV markers, the sensitivity of the analysis, the study population, and the availability of studies at different points in time are more likely to identify low-copy samples [3, 10]. Many studies have shown that HBV DNA is only occasionally detected in serum/plasma,

and when detected, its concentration is low, usually less than 200 IU/ml (about 1000 copies/ml) [8]. Due to the factors listed above, the prevalence of occult hepatitis B is difficult to summarize. It is most often observed in people with liver diseases, for example, in HBsAg–negative hepatocellular carcinoma, its frequency reaches 70 %, after liver transplantation reaches up to 64 %, and barely reaches 5 % in blood donors [8].

Increasing numbers of the modern literature sources suggest that in areas of medicine where immunosuppressive therapy is actively used, standard screening for infection by the main marker (HBsAg) does not provide sufficient assurance of the absence of an active infectious process in liver tissue [10]. Reactivation of viral hepatitis is particularly dangerous for cancer patients due to the need to interrupt chemotherapy and the high incidence of deaths. HBV reactivation can occur in 40 % of people with latent infection when using powerful immunosuppressive therapy. The issue has been studied in more detail in patients with oncohematological pathology, since they are at the highest risk (especially when using rituximab), but it is also described against the background of treatment of solid tumors [11]. At the same time, the issues of reactivation of latent HBV in cancer patients remain poorly understood [9].

The phenomenon of occult HBV infection is largely a diagnostic problem. The search for suitable diagnostic markers of occult form of HBV is actively continuing. In particular, test systems are being developed to determine the presence of covalently closed circular HBV DNA in liver tissues [10]. This study is considered the gold standard on which both the concept and diagnosis of occult hepatitis B are based. The importance of testing this marker is due to the fact that it is this form of DNA that allows the virus to remain inaccessible in liver tissue after functional healing and elimination of the virus from the blood. Covalently closed viral DNA in hepatocytes remains stable, difficult to detect and not yet available for medication therapy, while fully ready for replication, and it can resume at any time if the body's immune system weakens and cannot suppress it. However, in practice, the detection of this form of viral DNA in the liver is often inapplicable due to its invasive approach and lack of standardized methods [8].

The relatively new indicators correlating with the presence of an active infectious process in the liver include the determination of HBcore-related antigen. It is a composite antigen that includes three proteins: nuclear antigen (HBcAg), a nucleocapsid containing viral DNA; E-antigen (HBeAg), a circulating protein that is expressed from the core gene, then modified and secreted by liver cells; auxiliary precore-bound antigen (PreC), found in the virus-similar particles that do not contain DNA. In general, the HBcore-bound antigen is a surrogate marker of intrahepatic HBV replication, correlating with viral DNA and HBsAg levels, and can also serve as an additional marker for detecting infection phases [12, 13]. Other promising types of markers associated with the transcriptional activity of cccDNA virus in the liver include HBV RNA [14, 15] and quantification of anti-HBc levels [16]. However, such markers are not yet available in clinical practice.

Screening for anti-HBc in the blood as a surrogate marker is especially important both for donors and for people who are going to receive immunosuppressive therapy, since liver tissue is often unavailable, access to HBV DNA tests in the blood may be limited or delayed, and undetectable HBV DNA in the blood, tested in one the moment in time does not exclude the presence of infection. Indeed, HBV reactivation was recorded in HBsAg-negative and anti-HBc-positive individuals whose viral DNA was not detected in their blood. Taking into account that the detection of anti-HBc is not an absolute proof of the presence of a occult form of infection (since they continue to be detected even after full clearance of the virus), we have to admit that so far this remains one of the few available options for primary screening of the population for the prevalence of occult hepatitis B [10].

The World Health Organization's guidelines for the treatment of HBV, updated in 2024, also emphasize the importance of identifying the occult form of infection and the risk of its reactivation in patients with immunosuppressive therapy. HBV reactivation can occur spontaneously or can be caused by chemotherapy to lead to the fatal development of acute or chronic hepatitis, therefore, proactive therapy with nucleosi(t)de analogues is used [5].

The purpose of the study was to analyze the frequency of detection of HBsAg-negative hepatitis B serological and molecular biological markers among cancer patients.

MATERIALS AND METHODS

Blood samples of patients with oncological diseases who were admitted to the National Medical Research Center of Oncology, the Russian Federation Ministry of Health, in the period from 2016 to 2023 were examined. All patients signed an informed consent to participate in the study at the screening stage. HBsAg was determined (with a confirmatory test for positive samples), anti-HBcore was determined using enzyme immunoassay systems (Vector-Best JSC, Russia; recording of the results – Infinite F50, Tecan Austria GmbH, Austria) or the Vitros 3600 immunochemiluminescence analyzer (Ortho Clinical Diagnostics, USA). The sensitivity of the methods was at least 0.01 IU/ml.

A total of 41,523 blood serum samples of patients with HBsAg were examined, of which 26,724 were men, 14,799 were women, and the median age was 58 years. 2,035 samples were tested for total anti-HBcore (the study was assigned to people with onco-hematological diseases), of which 958 samples were simultaneously tested for HBsAg and anti-HBcore.

Additionally, 1,380 studies were performed on the presence of HBV DNA in blood plasma, reagent kits for the MagNAPure Compact automatic isolation station (Roche Diagnostics Ltd, Switzerland) were used to isolate DNA, AmpliSens HBV-FL was used to determine DNA, and AmpliSens HBV-monitor-FL was used for quantitative determination., Russia), the sample extraction volume was 1 ml. Amplification was performed by polymerase chain reaction (PCR) in real time with hybridization-fluorescence detection using a Rotor-Gene Q thermal cycler (Qiagen GmbH, Germany). The sensitivity of the method at an extraction volume of 1 ml for a qualitative test was 10 IU/ml, the linear measurement range for a quantitative test was within 15–100 000 000 IU/ml.

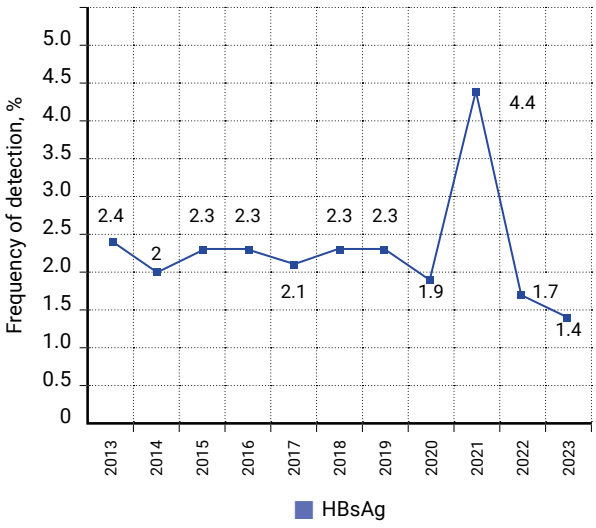

Fig. 1. Dynamics of HBsAg detection among cancer patients

Statistical analysis

Statistical data processing was carried out using the Microsoft Office Excel and STATISTICA 10.0 application software package. Descriptive statistics for categorical variables are presented in the form of absolute and relative frequencies (percentages, %). To study the relationship of categorical variables, the χ^2 test and the Fisher exact criterion were used, the association was considered statistically significant at $p < 0.05$.

STUDY RESULTS

The prevalence of HBsAg among cancer patients was 2.5 % (1051/41523, Fig. 1). It was found in men twice as often as in women: in 2.7 % of cases versus 1.1 % ($p = 0.0001$, $\chi^2 = 15.37$). The largest proportion of HBsAg-positive samples was detected in 2021 (4.4 %), the smallest in 2023 (1.4 %).

The frequency of HBsAg detection was also analyzed depending on the department profile: the 2 % prevalence threshold was exceeded in several of them, the highest frequency was for people with hematological diseases (Fig. 2).

The overall frequency of anti-HBcore detection ranged from 18.5 % (2022) to 27.1 % (2021) and averaged 23.7 % (483/2035, Fig. 3).

Simultaneous examination for HBsAg and anti-HBcore revealed various combinations of markers. Among the variants with at least one hepatitis B marker, "HBsAg- anti-HBcore+" turned out to be the most common. The number of such patients ranged from 15.9 % in 2022 to 24.5 % in 2016 and 2019, with an average of 20.6 % (197/958). The simultaneous presence of both markers was noted in an average of 4.6 % of patients (44/958): the maximum such variant was detected in 2017 (8.5 %), the minimum in 2019. (2,8 %). No isolated cases of HBsAg have been identified.

The total number of people with at least one HBV serological marker was 25.2 % (241/958). 81.7 % of

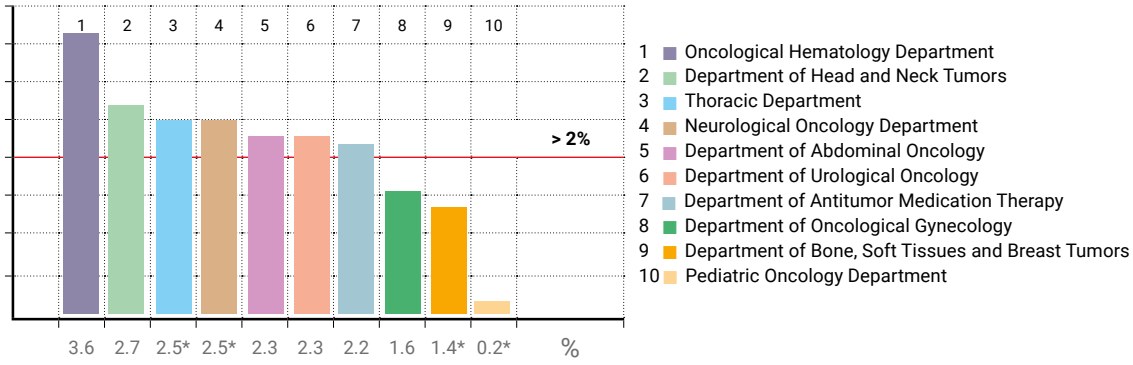

Fig. 2. Frequency of HbsAg detection depending on the department profile
Notes: * – statistically significant difference compared to the Department of Hematology ($p < 0.05$)

these turned out to be HBsAg-negative (197/241). Which means that during a standard screening examination, these patients would have remained undetected.

A study was also carried out for the viral DNA presence in the blood serum: a total of 219 positive samples were found. The viral load level was in a wide range of values: there were samples outside the linear measurement range (less than 15 IU/ml – 23.2 %, more than 100,000,000 IU/ml – 6.5 %), the median values within the linear range was 1020.0 IU/ml [148.5; 14084.0]. Of these, 19 samples were examined simultaneously for the presence of HBsAg, anti-HBcore. Taking into account the presence of viral DNA, the patient profiles were distributed as follows (Table 1).

The majority (78.9 %) had all three markers, which was regarded as a clear variant of the disease. HBsAg-negative, but DNA-positive was 21.1 %, which is a occult form of infection that could not be detected with standard screening. 15.8 % of this number were anti-HBcore-positive, and 5.3 % had no serological markers. As for the level of viral load, within the linear range, the median value was 413.0 IU/ml [389.0; 5968.0], 21.0 % had less than 15 IU/ml. Among the HBsAg-negative variants, 75.0 % (3/4) of patients had a viral load below the linearity limit, and one patient (25.0 %) had a viral load of 403 IU/ml.

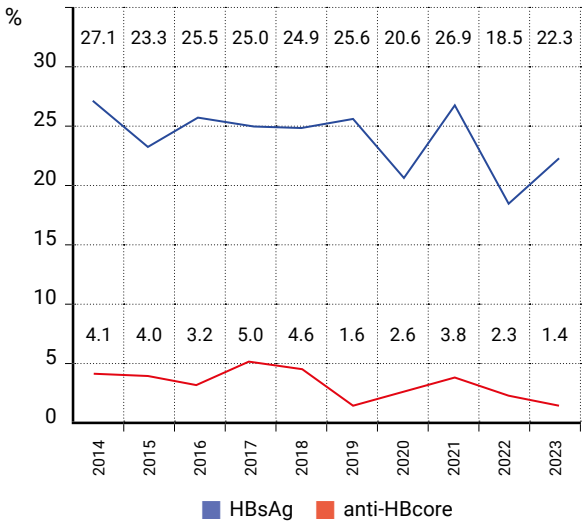

Fig. 3. Dynamics of HBsAg and anti-HBcore detection in oncohematological patients

DISCUSSION

According to our data, the prevalence of HBsAg among cancer patients was 2.5 % overall, which exceeds the detection rate in conditionally healthy individuals and donors (from 0.07 % to 0.25 %) and correlates with the available literature data [17]. The dynamics of the indicator was relatively stable with the exception of the one in 2021: during this period, there was an unexplained increase in other parameters of pre-hospital screening, including hepatitis C virus (HCV), human immunodeficiency virus (HIV) and syphilis.

There is evidence that in patients with a negative HBsAg test result, but with other markers of HBV infection (anti-HBcore IgG+, anti-HBs IgG+/-), the use of immunosuppressive therapy causes reactivation of chronic hepatitis with a typical serological and molecular biological profile of active infection (HBsAg+, anti-HBe IgG+, anti-HBcore IgG+, HBV DNA+, ALT↑↑). These data convincingly demonstrate the importance of dynamic monitoring of patients with occult form of hepatitis B [10]. If we talk about the experience of our institution, epi-

sodes of reactivation were also recorded in previous studies [18], in all cases all three markers were identified. A sharp increase in the viral load was noted, including to a value exceeding 100 million IU/ml. Patients received antiviral therapy along with antitumor treatment, as a result of which the majority of patients managed to reduce the viral load to undetectable, and only one patient failed to stabilize the situation, and chemotherapy was interrupted.

In the study of Semenenko T. A. et al. analysis of the results of serological testing revealed 13 hematological patients with HBV DNA, but with a different serological profile: five people with HBsAg–/HBV DNA+ (group 1) and eight people with HBsAg+/HBV DNA+ (group 2) [10]. The authors considered it important to note that HBV DNA was contained in very low concentrations (< 102 IU/ml) in the blood serum of patients negative for HBsAg, while in three cases (2.3 %) HBV DNA served as the only marker of HBV infection. In our study, the detected concentration of HBV DNA was also at a low level (less than 100 IU/ml) in the absolute majority of cases (75.0 %). These results are consistent with data from other researchers who have shown that the viral load in occult HBV infection is extremely low [8, 9].

It should be noted that the documents regulating the stages of hepatitis B diagnosis, which include recommendations from foreign and domestic oncological associations and clinical guidelines, do not mention occult forms of hepatitis B as such, but in most cases they all indicate the need to study additional markers besides HBsAg. In particular, in the recommendations of the American Society of Clinical Oncology (ASCO) and the National Comprehensive Cancer Network (NCCN), the volume of additional studies is determined depending on the therapy used and the associated risk [19, 20]. In addition to the degree of risk of the planned antitumor therapy, the serological status and the level of viremia are taken into account by the Russian Society of Clinical Oncology (RUSSCO) in the recommendations updated in 2023. In particular, it highlights the high incidence of patients who lack HBsAg in their blood, but at the same time anti-HBc is detected. For immunocompromised individuals, including those receiving antitumor treatment, the risk of HBV reactivation is: in the presence

Table 1. Variants of HBV marker combinations in oncohematological patients

The combination of markers	abs. / n	%	% out of positives at least to one HBV marker
Serological markers exclusively			
HBsAg+ anti-HBc+	44 / 958	4.6	18.3
HBsAg- anti-HBc+	197 / 958	20.6 $p^1 < 0.0001$ $\chi^2 = 111.11$	**81.7**
HBsAg- anti-HBc-	717 / 958	74.8 $p^1 < 0.0001$ $\chi^2 = 987.32$; $p^2 < 0.0001$ $\chi^2 = 565.70$	
Serological and molecular biology markers			
HBV DNA + HBsAg+ anti-HBc+	15 / 19	78.9	78.9
HBV DNA + HBsAg- anti-HBc+	3 / 19	15.8 $p^3 = 0.0001$ F = 0.40	**21.1**
HBV DNA + HBsAg- anti-HBc-	1 / 19	5.3 $p^3 < 0.0001$ F = 0.557	

Notes: abs. is the number of identified samples, *n* is the total number of examined, p^1 is a statistically significant difference compared to the "HBsAg+ anti-HBc+" variant, p^2 is a statistically significant difference compared to the "HBsAg- anti-HBc+" variant, p^3 is a statistically significant difference compared to the "HBV DNA+" variant. HBsAg+ anti-HBc+"

of anti-HBc – 5 %, and in the absence – in 14 % of patients. The risk of reactivation is higher in patients with oncohematological diseases: from 18 % in people with only antibodies to HBcore, up to 48 % in people with chronic HBV. In patients with solid tumors, the risk of HBV reactivation is ~3 % in patients with HBcore antibodies and up to 25 % in patients with chronic hepatitis B [11]. And the data we have obtained on such a high percentage of occult form of hepatitis B among cancer patients fully confirm the need for them to comply with more extensive screening, as shown in the recommendations mentioned above.

CONCLUSIONS

The detection of antibodies to HBcoreAg in the absence of HBsAg, as a rule, may indicate the presence of a occult form of hepatitis B, which, under conditions of drug immunosuppression, is capable of becoming active. The revealed significant percentage of cancer patients with a occult variant of hepatitis B is of concern and highlights the need to expand the number of diagnostic markers for screening. Additional testing for anti-HBcore and HBV DNA can significantly increase the likelihood of detecting HBV at the prehospital examination stage.

References

1. European Association for the Study of the Liver. EASL 2017 Clinical Practice Guidelines: management of chronic hepatitis B virus infection. J Hepatol. 2017;67(2):370–398. https://doi.org/10.1016/j.jhep.2017.03.021
2. Fazylov VKh, Yeremeyeva ZhG, Turayev RG. Latent hepatitis B diagnostic approach improvement in blood donors. Infectious Diseases: News, Opinions, Training. 2023;12(1(44)):54–61. (In Russ.). https://doi.org/10.33029/2305-3496-2023-12-1-54-61, EDN: VJKNLT
3. Zaytsev IA. Occult HBV infection. Aktual'naâ Infektologiâ. 2018;6(3):132–140. (In Russ.). https://doi.org/10.22141/2312-413x.6.3.2018.136646, EDN: UUTTKJ
4. You H, Wang F, Li T, Xu X, Sun Y, Nan Y, et al. Guidelines for the Prevention and Treatment of Chronic Hepatitis B (version 2022). J Clin Transl Hepatol. 2023 Nov 28;11(6):1425–1442. https://doi.org/10.14218/JCTH.2023.00320
5. World Health Organization. Guidelines for the Prevention, Diagnosis, Care and Treatment for People with Chronic Hepatitis B Infection (Text Extract): Executive Summary. Infect Dis Immun. 2024 Jul;4(3):103–105. https://doi.org/10.1097/ID9.0000000000000128
6. Terrault NA, Lok ASF, McMahon BJ, Chang KM, Hwang JP, Jonas MM, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology. 2018 Apr;67(4):1560–1599. https://doi.org/10.1002/hep.29800
7. Raimondo G, Allain JP, Brunetto MR, Buendia MA, Chen DS, Colombo M, et al. Statements from the Taormina expert meeting on occult hepatitis B virus infection. J Hepatol. 2008 Oct;49(4):652–657. https://doi.org/10.1016/j.jhep.2008.07.014
8. Raimondo G, Locarnini S, Pollicino T, Levrero M, Zoulim F, Lok AS, et al. Update of the statements on biology and clinical impact of occult hepatitis B virus infection. J Hepatol. 2019 Aug;71(2):397–408. https://doi.org/10.1016/j.jhep.2019.03.034
9. Semenenko TA, Yarosh LV, Bazhenov AI, Nikitina GYu, Kleimenov DA, Elgort DA, et al. Epidemiological evaluation of the prevalence of «occult» forms and epidemiological estimation of the «Occult» hepatitis b infection and hbsag-mutations prevalence at patients with hematological disease. Epidemiology and Vaccinal Prevention. 2012;(6(67)):9–14. (In Russ.). EDN: PUKKFT
10. Semenov AV, Ostankova YuV. Occult (latent) hepatitis B virus: problems of laboratory diagnostics. Infectious Diseases: News, Opinions, Training. 2019;8(3(30)):61–69. (In Russ.). https://doi.org/10.24411/2305-3496-2019-13010, EDN: MSJYRX
11. Feoktistova PS, Vinnitskaya YeV, Nurmukhametova YeA, Tikhonov IN. Practical recommendations for the prevention and treatment of reactivation/exacerbation of chronic viral hepatitis in patients receiving antitumor therapy. Practical recommendations of RUSSCO, part 2. Malignant Tumours. Russian Society of Clinical Oncology. 2023;13(#3s2):296–303. (In Russ.). https://doi.org/10.18027/2224-5057-2023-13-3s2-2-296-303
12. Tseng TC, Wu JW, Kao JH. Looking Into the Crystal Ball: A Novel Biomarker for Outcomes of Patients With Chronic Hepatitis B Virus Infection. Hepatol Commun. 2022 Jan;6(1):5–7. https://doi.org/10.1002/hep4.1856
13. Sandmann L, Bremer B, Ohlendorf V, Jaroszewicz J, Wedemeyer H, Cornberg M, et al. Kinetics and Value of Hepatitis B Core-Related Antigen in Patients with Chronic Hepatitis B Virus Infection during Antiviral Treatment. Viruses. 2024 Feb 5;16(2):255. https://doi.org/10.3390/v16020255

14. Carey I, Gersch J, Wang B, Moigboi C, Kuhns M, Cloherty G, et al. Pregenomic HBV RNA and Hepatitis B Core-Related Antigen Predict Outcomes in Hepatitis B e Antigen-Negative Chronic Hepatitis B Patients Suppressed on Nucleos(T)ide Analogue Therapy. Hepatology. 2020 Jul;72(1):42–57. https://doi.org/10.1002/hep.31026
15. Dahari H, Shlomai A, Cotler SJ. Early HBV RNA kinetics under NA treatment may reveal new insights into HBV RNA dynamics and NA mode of action-more detailed kinetic studies are needed. J Viral Hepat. 2021 Apr;28(4):687–688. https://doi.org/10.1111/jvh.13463
16. Shi Y, Wang Z, Ge S, Xia N, Yuan Q. Hepatitis B Core Antibody Level: A Surrogate Marker for Host Antiviral Immunity in Chronic Hepatitis B Virus Infections. Viruses. 2023 May 3;15(5):1111. https://doi.org/10.3390/v15051111
17. Bochkova GD, Ishchenkova IV, Palukhin SI, Kudinova EYe, Ryabikina EV, Gerasimova OV, et al. Frequency of detection of markers of hemotransmissive infections in donors of the Rostov region. Chief Physician of the South of Russia Magazine. 2019;(2(66)):4–6. (In Russ.). EDN: SCDRMP
18. Zykova TA, Nikolaeva NV, Kapuza EA, Pushkareva TF, Shatokhina OI, Velikorodnaya LA, et al. The effect of chemotherapy on the reactivation of chronic viral hepatitis B in patients with lymphomas. In the book: Materials of the IV St. Petersburg Oncological Forum "White Nights 2018" Abstracts. Autonomous non-profit scientific and medical organization "Issues of Oncology". 2018, 223 p. (In Russ.). EDN: UUPHOM
19. Hwang JP, Feld JJ, Hammond SP, Wang SH, Alston-Johnson DE, Cryer DR, et al. Hepatitis B Virus Screening and Management for Patients With Cancer Prior to Therapy: ASCO Provisional Clinical Opinion Update. J Clin Oncol. 2020 Nov 1;38(31):3698–3715. https://doi.org/10.1200/jco.20.01757
20. Prevention and Treatment of Cancer-Related Infections. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®). Version 1.2024 – April 30, 2024. Available at: https://www.nccn.org/professionals/physician_gls/pdf/infections.pdf

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