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Evaluation of Hepatitis B, C and HIV Seroprevalence in Lymphoma Patients

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Abstract

Objective: Hepatitis B and C viruses (HBV, HCV), as well as the Human Immunodeficiency Virus (HIV), are capable of replicating in lymphoid tissues. These infections can lead to chronic antigenic stimulation, which may be linked to the development of lymphoproliferative disorders. This study aims to explore the serological status of Hepatitis B, C, and HIV in lymphoma patients. ***Methods:*** In this study, medical records of lymphoma patients diagnosed between 2022 and 2024 were reviewed to record parameters such as HBsAg, Anti-HBs, Anti-HBc IgG, Anti-HCV, Anti-HIV. ***Results:*** The average age of the 59 patients was 60.6 ± 15.3 years, and 37.3% were women. Of the 59 patients, 41(69.5%) were treated with chemotherapy including Rituximab (rtx). Among the patients, 6 (10.1%) were HBsAg positive, 22 (37.2%) were HBsAg negative with Anti-HBc (+) detected. Of the 28 patients with HBsAg (+) and/or Anti-HBc IgG (+), 24 had received rtx treatment, and antiviral therapy was administered to 20 of them. One of these patients experienced HBV reactivation during follow-up. A false positive result for Anti-HCV was observed in one patient (1.7%). HIV positivity was detected in 3 patients (5%). ***Conclusıon*:** These findings indicate that the seroprevalence of Hepatitis B and HIV in lymphoma patients in our center is higher than in the general population. Therefore, HBV and HIV tests should be performed before initiating treatment in lymphoma patients. These patients should be evaluated for the risk of HBV reactivation, and appropriate prophylaxis should be planned.

Keywords: Lymphoproliferative diseases, HBV reactivation, immunosuppressive treatment, Rituximab, HIV prevalence.

INTRODUCTION

Lymphomas are predominantly sporadic, and their precise etiological causes remain unclear. Research suggests that genetic abnormalities, immunosuppression, radiation exposure, carcinogenic chemicals, and oncogenic viruses play a role in lymphoma etiology [1]. Hepatitis B and C viruses have the ability to proliferate within lymphoid tissues. "These viruses have the potential to cause chronic antigenic stimulation and may be associated with lymphoproliferative diseases [2]. Studies have highlighted the association of Hepatitis C virus (HCV) with the etiology of Non-Hodgkin lymphoma (NHL), with approximately 8% of NHL cases being attributed to HCV [3, 4]. Additionally, some studies suggest a role for HIV in the etiology of Diffuse Large B-Cell Lymphoma and T-cell lymphomas [5].

In addition, HBV reactivation in patients undergoing chemotherapy presents a significant problem in lymphoma patients, making HBV prophylaxis and/or vaccination essential. Our country, like other Mediterranean and Middle Eastern countries, is classified as an area of medium endemicity for HBV. In particular, lymphoma patients treated with B-cell-targeted anti-CD20 monoclonal antibodies, such as Rituximab, frequently encounter the risk of HBV reactivation or acute flare-ups of existing HBV infections. HBV flare-ups may lead to the discontinuation of chemotherapy and delay the treatment of the primary disease [6].

Current guidelines from EASL, APASL, AASLD, and AGA recommend pre-treatment screening for HBV serology in all patients undergoing high-risk B-cell-targeted therapy, with prophylaxis using agents like

ETV, TAF, or TDF advised for those who are HBsAg positive or HBsAg negative but Anti-HBc positive [7-9]. These guidelines also recommends active immunization for patients who are negative for HBsAg and Anti-HBs.

In this study, we aim to determine the seroprevalence of HBV, HCV, and HIV in lymphoma patients at our center, to evaluate the success rates of HBV prophylaxis in patients receiving high-risk B-cell-targeted therapy, and to emphasize the importance of prophylaxis.

MATERIAL AND METHODS

This study was conducted with the approval of the Ethics Committee for Clinical Researches at Hamidiye (09.11.2023/56).

Fifty-nine patients diagnosed with lymphoma between May 15, 2022, and May 15, 2024, with available serological test results, who visited Sultan 2. Abduhamid Han Training and Research Hospital were included in this study. All data were retrospectively collected through the hospital's electronic system.

The following parameters were reviewed for each patient: demographic features, lymphoma subtype, use of Rituximab or other immunosuppressive treatments, pre-treatment serological status for HBV, HCV, and HIV, biochemical parameters, use of prophylactic antiviral treatment, occurrence of HBV reactivation, and follow-up durations.

For HBsAg-positive patients, HBV reactivation was defined as either a 2 log10 IU/ml or greater increase in HBV DNA levels following immunosuppressive therapy in patients who initially tested positive for HBV DNA, or an HBV DNA level >100 IU/ml following immunosuppressive therapy in patients with unknown baseline HBV DNA levels. For HBsAg-negative, anti-HBc-positive patients, HBV reactivation was defined as either reverse seroconversion of HBsAg (conversion from HBsAg-negative to HBsAg-positive) following immunosuppressive therapy or the detection of HBV DNA in the serum post-therapy in patients who were initially HBV DNA-negative.

Serological and virological tests were performed on serum samples using the Electrochemiluminescence Immunoassay (ECLIA) method, utilizing fourth-generation kits (Roche Diagnostics, Germany) in accordance with the manufacturer's recommendations.

Statistical Analysis

Statistical analysis was performed using IBM SPSS version 22. The normal distribution of the data was assessed using the Shapiro-Wilks test. For difference analysis, chi-square tests were applied for categorical data, Student's t-test and ANOVA were employed for continuous data that met parametric assumptions, and Mann-Whitney U and Kruskal-Wallis tests were used for data that did not meet parametric assumptions. Statistical significance was evaluated at a confidence level of 95% ($p<0.05$).

RESULTS

The average age of the 59 patients included in the study was 60.6 ± 15.3 years, with 22 (37.3%) being female (Table 1). Of these patients, 15 were diagnosed with Hodgkin lymphoma (HL) and 44 with non-Hodgkin lymphoma (NHL). Forty-one of the 59 patients (69.5%) received chemotherapy containing Rituximab (rtx).

Six patients (10.1%) were HBsAg positive. Among these, three had Diffuse Large B-Cell Lymphoma (DLBCL), one had Follicular Lymphoma, and two had HL. No statistically significant difference was found between NHL and HL groups regarding HBsAg positivity ($p>0.05$).

Additionally, 22 patients (37.3%) were HBsAg negative but tested positive for Anti-HBc. Among patients with isolated anti-HBc positivity, 16 (72.7%) had anti-HBs positivity, which was interpreted as past hepatitis B infection. Eight patients (13.6%) were vaccinated against hepatitis B.

Prophylactic antiviral therapy (TDF: 2, TAF: 1, ETV: 17) was initiated in 20 of the 28 patients (24 of whom had received rituximab) with reactive Anti-HBc IgG and/or HBsAg. Four patients who received Rituximab but did not undergo antiviral treatment were found to be HBsAg negative, Anti-HBc IgG positive, and Anti-HBs positive. During follow-up, one of these patients developed HBV reactivation. This patient had been treated with Rituximab and was HBsAg negative and Anti-HBc IgG positive. No reactivation occurred in patients undergoing prophylactic antiviral therapy.

One patient (1.7%) had a false-positive Anti-HCV result (in classical HL). Three patients (5%) tested positive for Anti-HIV (two with DLBCL and one with Burkitt lymphoma) and were treated on ART.

Table 1: Clinical and demographic characteristics of the patients (n:59)

		n	%
Age, s		60,6 ± 15,3 year	
Gender	Female	22	37,3
	Male	37	62,7
Using rituximab		41	69,5
HBsAg	Reactive	6	10,1
	Non-reactive	53	89,9
HBsAg (-) Anti-HBc IgG (+)	Anti-HBs (+)	16	72,7
	Anti-HBs (-)	6	27,3
HBsAg (-) Anti-HBc IgG (-)	Anti-HBs (+)	8	25,8
	Anti-HBs (-)	23	74,2
HBV antiviral prophylaxis	TDF 245 mg/day	2	10
	TAF 25 mg/day	1	5
	ETV 0.5 mg/day	17	85
Diagnoses	DLBCL	23	39
	Mantle cell lymphoma	5	8,4
	Follicular lymphoma	9	15,3
	Marginal zone lymphoma	3	5,1
	CLL	2	3,4
	Burkitt lymphoma	2	3,4
	Hodgkin lymphoma	15	25,4

DLBCL: Diffuse large B cell lymphoma, CLL: Chronic Lymphocytic Leukemia, TDF: Tenofovir disoproxil fumarate, TAF: Tenofovir alafenamide, ETV: Entecavir

DISCUSSION

The course of HBV infection in lymphoma patients is closely linked to the patient's immune status and the mechanisms of action of the immunosuppressive drugs administered during treatment. Although incorporating rituximab into standard chemotherapy regimens has been demonstrated to enhance treatment outcomes in patients with NHL, it also introduces a risk for HBV flare-ups and disease exacerbation in individuals with a history of HBV infection. HBV reactivation commonly occurs following the restoration of the host's immune function, typically during chemotherapy cycles or at the conclusion of treatment. In our study, 69.5% of patients received chemotherapy regimens that included rtx. A study by Torres HA *et al*., reported that, in HBV carriers, particularly those undergoing chemotherapy with monoclonal antibodies like rituximab, HBV reactivation was observed in up to 70% of cases, with mortality rates ranging from 5% to 50% [10]. When reactivation occurs, delaying or halting chemotherapy can have a detrimental effect on patients' survival outcomes. The prophylaxis of HBsAg-negative/Anti-HBc-positive patients with hematological malignancies remains a subject of ongoing discussion, and one study suggests mandatory prophylaxis in patients receiving rituximab-based chemotherapy due to the potential risk of occult HBV reactivation [11]. In a study by Türe *et al*., which included 107 patients who underwent hematopoietic stem cell transplantation, antiviral prophylaxis was administered to 52.6% of patients deemed at high risk for HBV. In our study, prophylactic antiviral treatment (TDF: 2, TAF: 1, ETV: 17) was initiated in 20 out of 28 patients (24 of whom received rituximab), all of whom were positive for either HBsAg or Anti-HBc IgG. This rate of prophylactic antiviral treatment initiation in our cohort was notably higher. Among four patients who received rituximab but did not undergo antiviral treatment, laboratory tests showed HBsAg negative, Anti-HBc IgG positive, and Anti-HBs positive. During follow-up, one of these patients developed HBV reactivation. This finding indicates that HBV reactivation occurred in one of the four patients following rituximab, with the observed flare-up rate aligning with that reported in the literature. The patient's positive Anti-HBs titre did not prevent the reactivation during the flare-up. The absence of reactivation in any patient who received prophylactic antiviral treatment highlights the crucial role of prophylaxis. No reactivation was observed in patients treated with ETV, TDF, or TAF, suggesting that these treatments may be effective in preventing reactivation. Nevertheless, we believe that further studies involving larger patient populations are necessary to validate these findings. Additionally, the higher frequency of ETV use in our study may be attributed to its relatively lower risk of drug interactions.

In a study conducted on adults in our country, the prevalence of HBsAg positivity was reported as 4% [12]. In our study, however, HBsAg positivity was found to be 10.1%. This may be attributed to the higher average age of our patients and the fact that a large portion of the study population was born before the childhood HBV vaccination program was initiated in Turkey in 1998. Therefore, it is essential to screen all patients for HBV upon a lymphoma diagnosis and to evaluate those with a

history of HBV infection for antiviral prophylaxis prior to chemotherapy.

Additionally, our study revealed that only 25.8% of patients had received the HBV vaccine, and a large proportion of patients were not vaccinated. Given the risk of reactivation in lymphoma patients, we emphasize the vital importance of HBV vaccination and the need for a more proactive approach in this regard.

In a study, the prevalence of Anti-HCV positivity in NHL patients was found to be 3.7%, and in HL patients, it was 2.7%. It was suggested that this virus could play a role in lymphoma etiology and that there is a lack of awareness regarding this infection [13]. In our study, one patient showed a false positive for Anti-HCV. This could be due to the effective HCV treatment strategies and new drugs in our country, which have likely reduced HCV seroprevalence.

The heterogeneity of lymphoma in individuals infected with HIV is likely related to the complexity of the underlying pathogenic mechanisms (HIV-induced immunosuppression, genetic abnormalities, cytokine dysregulation, co-infection with Epstein-Barr virus and Human Herpesvirus 8), and irregularities in the immune responses controlling these viruses. Diffuse large B-cell lymphoma is one of the most common malignancies among individuals infected with HIV [14]. In our study, three patients (5%) were found to be Anti-HIV positive, indicating a significantly higher HIV seroprevalence than in the general population. These findings support the role of HIV in lymphoma etiology. Two of these patients were diagnosed with DBBHL and one with Burkitt lymphoma, and our results were consistent with the literature.

Limitations of our study include the inability to determine the exact time between hepatitis virus infection and lymphoma development, the lack of homogeneity in the distribution of disease subtypes, and the relatively small number of patients.

CONCLUSION

In our center, the seroprevalence of HBV and HIV in lymphoma patients was found to be higher than in the general population. Screening for HBV and HIV co-infection before starting treatment in lymphoma patients is of critical importance. Starting antiviral prophylaxis for HBV seropositive cases and vaccinating unvaccinated patients as part of the program will be beneficial.

Author's Contributions:

BS: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Project administration, Resources, Software, Supervision, Validation, Visualization, Writing – original draft, Writing–review & editing, **RAC:** Conceptualization, Data curation, Resources, Software, Supervision, Validation, Visualization, Writing – original draft.

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