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HCV prevalence in Hodgkin and non-Hodgkin lymphoma cases

Hodgkin ve non-Hodkin lenfoma olgularında HCV prevalansi

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Background/aims: *In this study we aimed to investigate the relation between hepatitis C virus (HCV) and B cell lymphoproliferative diseases.* ***Methods:*** *Eighty-four patients with B-cell non-Hodgkin lymphoma and 50 patients with Hodgkin lymphoma were included. Control group consisted of another 100 otherwise healthy blood donors who had no previous history of invasive surgery, blood transfusions, and viral hepatitis. HCV positivity was investigated in both case groups and control group.* ***Results:*** *Anti-HCV positivity was significantly more frequent in B-cell non-Hodgkin lymphoma patients compared to control group (7.1% vs. 1%, p<0.05). In Hodgkin lymphoma patients however, frequency was comparable with the control group (2% vs. 1%, p<0.05).* ***Conclusions:*** *These findings suggest that HCV may play a role in the development of B-cell non-Hodgkin lymphoma, but not in Hodgkin lymphoma.*

Key words: Hapatitis C virus, B cell lymphoproliferative disease, Hodgkin lymphoma, B-cell non-Hodgkin lymphoma

Amaç: Bu çalışmamızda HCV ile B hücreli lenfoproliferatif hastalıklar arasındaki ilişki araştırıldı. ***Yöntem:*** *Çalışmaya B hücreli lenfoproliferatif hastalıklar li hasta gurubundan olan B hücreli lenfoproliferatif hastalıklar 84 hasta, non B hücreli lenfoproliferatif hasta gurubundan olan Hodgin lenfomalı 50 hasta dahil edildi ve bu hastalarda anti-HCV pozitifliğine bakıldı. Kontrol gurubu olarak ise daha önce invaziv girişim ve kan transfüzyonu uygulanmamış, geçmişinde viral hepatit öyküsü olmayan 100 sağlıklı kan donöründe anti-HCV pozitifliğine bakıldı.* ***Bulgular:*** *Anti-HCV pozitifliği B hücreli lenfoproliferatif hastalarında, kontrol grubu ile karşılaştırıldığında, anlamlı olarak daha sık gözlenmiştir (7.1% vs. 1%, p<0.05). Hodgkin lenfoma hastalarında ise sıklık kontrol grubu ile benzerdir (2% vs. 1%, p<0.05). Sonuç: Bu bulgular HCV'nin B hücreli lenfoproliferatif hastalıklar gelişiminde bir rolü olabileceğini düşündürmektedir.*

Anahtar kelimeler: Hepatit C virüsü, B hücreli lenfoproliferatif hastalıklar, Hodgin lenfoma, B-hücreli non-Hodgin lenfoma

INTRODUCTION

Recent studies have confirmed that hepatitis C virus (HCV) is not only a hepatotropic, but also a lymphotropic and sialotropic virus (1). This virus can be isolated from hepatocytes, hepatic lymphocytes, peripheral mononuclear cells, bone marrow and lymphoid tissues in infected people.

Particles of viral genome were found in T and B cells of patients with chronic hepatitis and infected with HCV (2). Recently, HCV infection was found in most of the type 2 mix cryoglobulinemia patients. This is a lymphoproliferative disease of the gland characterized by heat sensitive protein complexes derived from polyclonal Ig G and monoclonal Ig M. It is known that it progresses to B-cell non-Hodgkin lymphoma (NHL) in some cases (1). In rare B lymphocyte neoplasms associated with monoclonal Ig M production (Waldenstrom's macroglobulinemia), HCV infection is found in substantial proportion of cases, indicating a possible role for the virus in neoplastic Ig M gammopathies (3). Recent finding of HCV genome and anti-HCV in the sera of B-NHL cases not associated with mixed cryoglobulinemia suggests that HCV may be responsible for B cell-clonal proliferation.

Studies have demonstrated that hepatitis B is a moderately lymphotropic disease. The observation that the frequency of anti-HCV positivity in

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B-cell lymphoproliferative disease B-LPD patients is higher compared to non-B-LPD patients, who have a frequency similar to controls, has led to the assumption that the association between B-LPD and HCV is not coincidental and the virus can trigger one or more of the steps of B-LPD development. (1, 3, 4-6)

In addition, mainly hepatitis C genotype 2 was detected in B-LPD patients, while genotype lb was found in small amounts and genotypes la and 3 were not found at all (1). In the light of these findings, it was suggested that genotype 2ac might play a role in lymphoproliferative diseases and autoimmune diseases. Immune system, mutation, reproduction rate of the virus, genetic and environmental factors determines the presentation form of Hepatitis C, ranging between a benign infectious disease and a malign B-LPD.

In this study, we aimed to determine whether anti-HCV positivity is more frequent in B-LPD cases compared to controls. We also aimed to provide epidemiological data for Turkey regarding this issue.

MATERIAL AND METHODS

Anti-HCV positivity in a total of 134 patients was investigated. These cases consisted of two separate groups of patients (HL: Hodgkin lymphoma, B-NHL: B-cell non-Hodgkin lymphoma) admitted to SSK Okmeydani Training Hospital, Hematology and Oncology Clinic. B-LPD group (B-NHL) consisted of 84 cases (36 female, 48 male, age range: 36-71 years). Non-B-LPD group (HL) had 50 patients (30 female, 20 male; age range: 23-69 years). 17 NHL cases and 13 HL cases had a history of previous blood transfusions, and 35 NHL and 24 HL cases had history of previous surgery. Control group consisted of another 100 otherwise healthy blood donors who had no previous history of surgery, blood transfusions, or viral hepatitis (40 male, 60 female; age range: 17-64 years).

Anti-HCV analyses were conducted in SSK Okmeydani Hospital (Istanbul, Turkey), ELISA laboratory with a Core Cobas Immunoassay device. Third generation ELISA kits have been used for measurements. An experiment based on recombinant antigens in which antibodies against HCV were recognized was used.

In this experiment, serum and plasma samples are added into micro-boxes coated with antigens derived from HCV. These micro-surface micro-boxes are rinsed and then an anti-human immunoglobulin derived from goat that is labeled with wild radish peroxidase is added. In the presence of antigen-antibody complexes, peroxidase conjugate remains in the micro-box, as it is bound to the complex. During incubation, a blue color is observed in the cluster of anti-HCV antibodies bound to micro-boxes. On the other hand, no color change is observed in micro-boxes that contain samples without anti-HCV. An acid stop solution is added to each micro-box and absorption is read by a micro-surface absorptiometer at 450 nm (2,7-9).

The statistical data analysis was performed with SPSS 5.0 software for Windows, and chi-square, Fisher's exact chi-square, and analysis of variance were used for statistical assessments.

RESULTS

Anti-HCV positivity was evaluated in a total of 134 patients, who were either admitted to or followed as outpatients in SSK Okmeydani Training Hospital, Hematology and Oncology Clinic. In addition, HCV positivity was assessed in 100 healthy blood donors without previous history of invasive intervention, blood transfusion or viral hepatitis.

Eighty-four patients with B-NHL from B-LPD group, and 50 patients with HL from non B-LPD group were included in the study. The frequency of anti-HCV positivity was 7.1% and 1% in B-NHL patients and controls, respectively; this difference was significant ($p < 0.05$). The corresponding figure for HL patients was 2% ($p > 0.05$) and this finding was not statistically significant (Table 1) (Figure 1).

Table 1. Incidence of Anti-HCV among groups

	*HL	B-NHL		Control				
	N	%	p	N	%	P	N	%
Anti-HCV (-)	49	**98**	**0,1**	**78**	**92,9**	**0,04**	**99**	**99**
Anti-HCV (+)	1	**2**		**6**	**7,1**		**1**	**1**

* HL: Hodgkin lymphoma
B-NHL: B cell non hodgkin lymphoma

DISCUSSION

The objective of our study was to investigate the relationship between HCV infection and B-LPD. The incidence of anti-HCV positivity in B-NHL patients from B-LPD group was 7.1%. The incidence in control group was 1%. The frequency

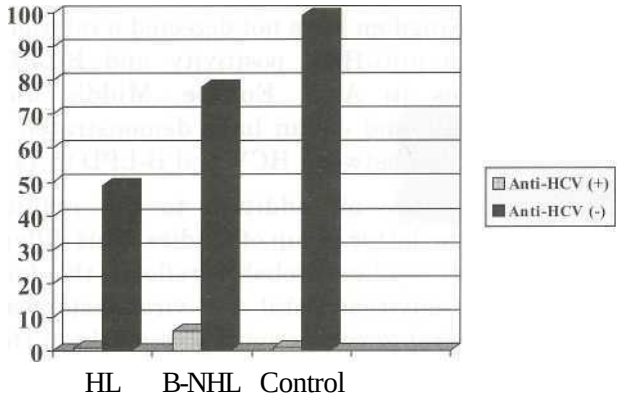

Figure 1. Incidence of Anti-HCV among groups

reported in the literature for a similar group of patients is 23.5%, and the figure reported for controls, which were healthy blood donors, is 5.4% (1, 5). Our results are comparable with literature data and demonstrate a significant difference. Various studies conducted in Turkey with blood donors have already revealed similar anti-HCV positivity rates with our control group (10-13).

The frequency of anti-HCV positivity in HL patients from non B-LPD group was 2%. The figures reported in the literature for the same group of patients is between 1 and 9%, similar to frequency in controls in the same studies (1,5).

In two other studies, the incidence of anti-HCV positivity in patients with B-NHL were 34% (14) and 20.8% (15).

Results from a variety of studies and our findings demonstrate that the frequency of anti-HCV positivity is higher in patients with B-LPD (B-NHL) compared to patients with non-B-LPD (HL), who show a frequency similar to that of controls. These observations have led to the assumption that the association between B-LPD and HCV is not coincidental and that the virus can trigger one or more of the steps of B-LPD development (1, 4, 5, 14-17), generating many hypotheses on the issue, including the following: In chronic liver diseases, persistent stimulation effect of HCV infection on lymphocytes in the liver may lead to the expansion of lymphoid clones, hence facilitating further mutations and transformations. As an alternative, a possible direct pathogenic effect of HCV on lymphoid cells is suggested. Finally, a predisposition of B-LPD patients to HCV infections may be suggested. However, several studies have already confirmed that this association is not coincidental, since anti-HCV positivity is often detected at the time of diagnosis in patients with B-LPD and these type of hematological disorders rarely require treatment with blood products (4,5)

Arican et al. from Turkey conducted a study to describe the relation between HCV infection and lymphoproliferative diseases and investigated the prevalence of hepatitis C virus and G virus (HGV) among NHL patients without any previous history of blood transfusion (18). HCV was found in 2 of 44 NHL cases, whereas HGV was not detected in any cases.

Paydas et al. (19) conducted a study in southern part of Turkey and found a HCV positivity rate of 11.4% among 228 cases with lymphoproliferative diseases. These findings support those of our study suggesting that HCV triggers lymphoproliferative diseases.

Kaya et al. (20) (Turkey) obtained findings quite different than ours. They investigated the presence of HCV and HGV among 70 NHL cases and results were not statistically different from controls. They suggested that neither HCV nor HGV has a role in the etiopathogenesis of NHL.

Salem et al. (21) conducted a study in Lebanon, a country in the same geographical region with Turkey, with B-cell NHL cases and obtained contradictory results from ours. They could not provide sufficient evidence for the role of HCV in the development of B-cell NHL.

Aviles et al. (22) (Mexico) supported the findings of Salem et al. Association of HCV and NHL may be explained with the high prevalence of HCV infection in the general population.

Shirin et al. (23) investigated HCV prevalence among cases with lymphoproliferative and myeloproliferative diseases and compared the results with healthy controls. In cases with lymphoproliferative diseases, particularly cases with diffuse large cell lymphoma, HCV rate was higher compared to the control group; however, such a difference could not be demonstrated for cases with myeloproliferative diseases.

Association of B-cell lymphoma and HCV shows variability across different geographical regions and ranges between 7.4% and 37%. It is suggested that HCV does not affect the course of B-cell NHL and its response to chemotherapy. Antiviral treatment for low grade HCV associated lymphoma is still controversial. However, encouraging results

have been obtained recently (24).

Studies have shown that the high frequency of anti-HCV positivity is independent of the blood transfusions performed and the time elapsed from the diagnosis when these parameters were adjusted for (4,5). Our findings support the view that blood transfusions were not related to anti-HCV positivity ($p > 0.05$).

Overall, these findings suggest that HCV may play a role in lymphoproliferative diseases and autoimmune disease. HCV may be associated a wide range of diseases from a benign infection to **B-LPD** depending on factors like the immune status of the/infected person, the mutations and replication rate of the virus (1).

On the other hand, studies in the United States and United Kingdom have not detected a relationship between anti-HCV positivity and B-LPD, while studies in Asia, Europe, Middle and Northern Italy, and Japan have demonstrated a close association between HCV and B-LPD (5,14).

Our findings are an addition to the results observed in the latter group of studies. This difference between studies probably reflects the fact that genetic, environmental and viral factors as well as the viral genotype may play a role in the complex relationship between the patient and the virus. Further studies with larger patient populations investigating the prognostic profile of HCV infection and the treatment response will help to clarify this issue.

REFERENCES

1. Silvestri F, Barillari G, Fanin R, et al. The genotype of the hepatitis C virus in patients with HCV-related B cell non-Hodgkin's lymphoma. Leukemia 1997; 11: 2157-61.
2. Choo QL, Kuo G, Weiner AJ, et al. Isolation of a cDNA clone derived from a blood-borne non-A, non-B viral hepatitis genome. Science 1989; 244: 359-62.
3. Sansonno D, De Vita S, Cornacchiulo V, et al. Detection and distribution of hepatitis C virus-related proteins in lymph nodes of patients with type II mixed cryoglobulinemia and neoplastic or non-neoplastic lymphoproliferation. Blood 1996; 88: 4638-45.
4. Luppi M, Grazia Ferrari M, Bonaccorsi G, et al. Hepatitis C virus infection in subsets of neoplastic lymphoproliferations not associated with cryoglobulinemia. Leukemia 1996; 10: 351-5.
5. De Rosa G, Gobbo ML, De Renzo A, et al. High prevalence of hepatitis C virus infection in patients with B-cell lymphoproliferative disorders in Italy. Am J Haematol 1997; 55: 77-82.
6. Pivetti S, Novarino A, Merico F, et al. High prevalence of autoimmune phenomena in hepatitis C virus antibody positive patients with lymphoproliferative and connective tissue disorders. Br J Haematol 1996; 95: 204-11.
7. Alter HJ, Prince AM. Transfusion-associated non-A, non-B hepatitis: an assessment of the causative agent and its clinical impact. Transfus Med Rev 1988; 2: 288-93.
8. Harada S, Watanabe Y, Takeuchi K, et al. Expression of processed core protein of hepatitis C virus in mammalian cells. J Virol 1991; 65: 3015-21.
9. Sehulster LM, Hollinger FB, Dreesman GR, et al. Immunological and biophysical alteration of hepatitis B virus antigens by sodium hypochlorite disinfection. Appl Environ Microbiol 1981; 42: 762-7.
10. Yenice N, Çolakoğlu Ö, Gül K, Canoruç F. [Prevalence of Hepatitis C virus among blood donors in Diyarbakir.] Gastroenteroloji 1993; 4: 41-2.
11. Sırmatel F, Baydar İ. [Demostration of HBV and HCV carriers with ELISA among risk groups in Gaziantep region]. Viral Hepatitle Savasim Derneği III. Viral Hepatit Sempozyumu Program ve Kongre Kitabi ,Istanbul 1996; P: 49.
12. Kocazeybek B, Erentürk S, Sönmez B, et al. (Prospective 3 years evaluation of anti-HCV prevalanca among blood donors: comparison of seropositive sera with RIBA and PCR). Türk Mikrobiyoloji Cemiyeti Dergisi 1995; 25: 135-141.
13. Özdemir R, Kestellioğlu F, Kurultay N, et al. [Investigation of anti-HCV among 192 cases admitted to İzmir Atatürk Devlet Hastanesi Kan Merkezi between 1.10.1993-30.11.1993.] XXVII. Türk Mikrobiyoloji Kongre Kitabı, Antalya 1994; P: 263.
14. King PD, Wilkes JD, Diaz-Arias AA. Hepatitis C virus infection in non-Hodgkin's lymphoma. Clin Lab Haematol 1998; 20: 107-10.
15. Musolino C, Campo S, Pollicino T, et al. Evaluation of hepatitis B and C virus infections in patients with non-Hodgkin's lymphoma and without liver disease. Haematologica 1996; 81: 162-4.
16. Ferri C, La Civita L, Monti M, et al. Chronic hepatitis C and B-cell non-Hodgkin's lymphoma. QJM 1996; 89: 117-22.
17. Santini GF, Giannini F, Crovatto M, et al. HCV and lymphoproliferative diseases. Clin Exp Rheumatol 1995; 13 (Suppl 13): S51-7.
18. Arican A, Sengezer T, Bozdayi M, et al. Prevalence of hepatitis-G virus and hepatitis-C virus infection in patients with non-Hodgkin's lymphoma. Med Oncol 2000; 17: 123-6.
19. Paydaş S, Kilic B, Sahin B, Bugdayci R. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders in Southern Turkey. Br J Cancer. 1999; 80: 1303-5.
20. Kaya H, Polat MF, Erdem F, Gundogdu M. Prevalence of hepatitis C virus and hepatitis G virus in patients with non-Hodgkin's lymphoma. Clin Lab Haematol 2002; 24: 107-10.
21. Salem Z, Nuwaiyri-Salti N, Ramlawi F, et al. Hepatitis C virus infection in Lebanese patients with B-cell non-Hodgkin's lymphoma. Eur J Epidemiol 2003; 18: 251-3.
22. Aviles A, Valdez L, Halabe J, et al. No association between lymphoma and hepatitis C virus. Med Oncol 2003; 20: 165-8.
23. Shirin H, Davidovitz Y, Avni Y, et al. Prevalence of hepatitis C virus infection in patients with lymphoproliferative disorders. Isr Med Assoc J 2002; 4: 24-7.
24. Zuckerman E, Zuckerman T. Hepatitis C and B-cell lymphoma: the hemato-hepatologist linkage. Blood Rev 2000; 16 (2): 119-25.