Prevalence of Hepatitis C Virus Infection in Patients with Lymphoproliferative Disorders

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Abstract

Background: Epidemiologic studies in different parts of the world have revealed controversial results on the association between hepatitis C virus infection and non-Hodgkin's lymphoma. This discrepancy suggests that HCV lymphotropism or its effect on host lymphocytes may be influenced by regional and racial factors, as well as by genomic variations.

Objective: To determine the prevalence of HCV infection in patients with lymphoproliferative disorders diagnosed and treated in our institute in Israel.

Methods: A total of 212 consecutive patients (95 males and 117 females) treated in our hematology outpatient clinic between August 1997 and September 1999 was screened for anti-HCV antibodies and hepatitis B surface antigen. HCV infection was confirmed by the presence of HCV RNA in the serum. The prevalence of HCV in patients with lymphoproliferative disorders was compared to that in a control group of patients with myeloproliferative disorders and myelodysplastic syndromes.

Results: HCV infection was more prevalent in the group of LPD patients than in the control group, but this finding was not statistically significant. The prevalence of HCV among LPD patients was 7.8%, while that in the group with myeloproliferative and myelodysplastic disorders was 1.19% and in the general population 0.64%. Among the different classes of LPD, a significant association with HCV infection was established only in patients with diffuse large B cell lymphoma. Furthermore, HCV infection was significantly more prevalent than HBV infection in the LPD group, but not in the myeloproliferative and myelodysplastic disorders group.

Conclusions: Our finding of a significant association between HCV infection and diffuse large B cell lymphoma leads us to suggest that anti-HCV antibodies be performed routinely in such subjects.

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HCV = hepatitis C virus
LPD = lymphoproliferative disorders

Hepatitis C virus, a hepatotropic and lymphotropic virus, is linked to essential mixed cryoglobulinemia [1–3]. This clonal expansion of lymphocytes may in fact be a low grade lymphoma [4,5]. The association of HCV infection with essential mixed cryoglobulinemia, and of essential mixed cryoglobulinemia with lymphoproliferative disorders led to the assumption that HCV might be a causative agent in non-Hodgkin's lymphoma. Epidemiological studies undertaken in different parts of the world (Italy, Japan, Turkey, the USA) revealed a non-random association between HCV infection and non-Hodgkin's lymphoma [6–12], while others (Britian, Germany, Scotland, Midwest USA) failed to establish such an association [13–18]. Therefore, it has been suggested that the association may depend on regional and racial factors, as well as on HCV genotypic variations in different parts of the world.

The aim of the present study was to determine the prevalence of HCV infection among patients with lymphoproliferative disorders treated in our medical center in Israel. We compared the HCV seropositivity in the LPD group to the prevalence of HCV infection among patients with other hematologic diseases and to the prevalence of hepatitis B virus among LPD patients.

Patients and Methods

Patients

A total of 212 consecutive patients (95 males and 117 females) attending the hematology clinic at the Wolfson Medical Center between May 1997 and September 1999 was screened for anti-HCV antibodies and hepatitis B surface antigen. These patients suffered from the following hematologic malignancies: a) lymphoproliferative disorders (128 patients), including chronic lymphocytic leukemia/small lymphocytic lymphoma, follicular lymphoma, and diffuse large B cell lymphoma; and b) myeloproliferative and myelodysplastic disorders (84 patients).

The distribution of specific disorders (according to the REAL classification), median age and gender is given in Table 1. On the assumption that the ethnic distribution of the population in our district represents the ethnic distribution of the population of Israel, we used the data on Israeli blood donors published by Bar-Shany et al. [19] as the prevalence of HCV in the healthy population.

Detection of HCV and HBV infection

Anti-HCV antibodies and HbsAg were detected by MEIA (Microparticle Enzyme Immunoassay), AxSYM (HCV version 3.0 and HbsAg), Abbott, USA. Patients positive for HCV antibodies were tested for HCV RNA by a reverse-transcriptase polymerase chain reaction assay (COBAS AMPLICOR™, Roche, Switzerland). Patients were considered HCV-infected only if they showed findings positive for both HCV antibodies and HCV RNA.

Cryoglobulin analysis

Venous blood samples were collected from patients after an overnight fast into pre-warmed tubes and allowed to clot at 37°C. After centrifugation at 1,800 x g for 5 minutes, sera were incubated at 4°C for 48 hours. The cryocrit was evaluated by centrifugation of the serum in hematocrit tubes at 4°C, 1,800 x g for 5 min.

Statistics

The prevalence (%) of HCV and HBV infection among patients in the various groups was determined by dividing the number of patients positive for HCV-RNA PCR or HbsAg (respectively) in each group into the total number of patients in the same group, multiplied by 100. The significance of the differences in prevalence was estimated using the Fisher exact test. $P < 0.05$ was considered significant.

Table 1. Distribution of sex and median age in LPD and controls

Diagnosis	Distribution of LPD group			
	Total	Male	Female	Median age
LPD				
Chronic lymphocytic leukemia/small cell lymphocytic lymphoma	69	29 (42%)	40 (58%)	67
Diffuse large B cell lymphoma	36	13 (36%)	23 (64%)	67
Follicular lymphoma	23	13 (56%)	10 (44%)	59
Total	128	55 (43%)	73 (57%)	67
Myeloproliferative and myelodysplastic disorders				
Myelodysplastic syndrome	20	14 (70%)	6 (30%)	76
Polycythemia vera	35	17 (49%)	18 (51%)	62
Essential thyombocythemia	15	6 (40%)	9 (60%)	62
Myelofibrosis	7	5 (71%)	2 (29%)	58
Chronic myeloid leukemia	7	5 (71%)	2 (29%)	59
Total	84	47 (56%)	37 (44%)	66

Table 2. Prevalence of HCV and HBV infection in LPD and controls

	Patients total	HCV patients (prevalence)	P*	HBV patients (prevalence)	P**
Myeloproliferative and myelodysplastic disorders	84	1 (1.1%)		0 (0%)	
LPD, total	128	10 (7.8%)	0.053	1 (0.8%)	0.032
Chronic lymphocytic leukemia/small cell lymphocytic lymphoma	69	3 (4.3%)	0.328	1 (1.5%)	0.369
Diffuse large B cell lymphoma	36	5 (15.2%)	0.007	0 (0%)	0.006
Follicular lymphoma, total	23	2 (9.5%)	0.101	0 (0%)	0.182

* HCV prevalence

** HBV prevalence.

Results

Patients

Patients in the LPD group were matched for age and gender with those in the control group [Table 1]. They were also matched with respect to the percentage of those born in the former Soviet Union (14.1% in the LPD group, 10.7% in the control group), while in the group of blood donors in Israel, former USSR origin was recorded only in 1.1% [19]. It should be pointed out that the prevalence of HCV infection is much higher in the population that immigrated to Israel from the former USSR than in the general population [19].

HCV infection

None of the HCV-infected patients, except one, manifested signs, symptoms or liver function disturbances attributed to liver disease, and none of them had cryoglobulinemia. The only patient with overt liver disease (cirrhosis as confirmed by liver biopsy) had low grade lymphoma. In all the other HCV-positive LPD patients, the HCV infection was identified simultaneously with the diagnosis of LPD.

The prevalence of HCV infection in the two groups is shown in Table 2. The prevalence was higher in the LPD group (7.8%) than in the control group but a statistically significant difference could not be established. Although the prevalence of HCV infection within the sub-classes of LPD was also higher than in the control group, a significant difference could only be found in the patients with diffuse large B cell lymphoma ($P = 0.007$).

The prevalence of HCV antibodies in blood donors (a rough estimation of the prevalence in the Israeli population) was 0.66% for men and 0.55% for women. The prevalence in blood donors born in the former USSR was 3.01% for men and 1.64% for women [19]. The impression that the prevalence of HCV infection was higher in LPD patients than in the general population could not be statistically validated due to differences in age and ethnic origin.

HBV infection

The prevalence of HBV infection was similar in the LPD group (0.8%), control group (1.5%), and in blood donors in Israel

HBV = hepatitis B virus

HbsAg = hepatitis B surface antigen

(0.84% in men, 0.46% in women) [19]. In the LPD patients as a group, and particularly in patients with diffuse large B cell lymphoma, the prevalence of HCV infection was significantly higher than of HBV infection (P = 0.032 and P = 0.006 respectively). The difference was not statistically significant in other sub-classes.

Discussion

In the present study, HCV infection was demonstrated in 7.8% of patients with LPD, a much higher prevalence than in the healthy Israeli population. Since in all cases but one the infection was detected at the time of diagnosis, the possibility of HCV superinfection following treatment of the lymphoproliferative disorder can be excluded.

The prevalence of HCV differed in various classes of LPD, being highest among patients with diffuse large B cell lymphoma (15.2%). Compared to the prevalence in a matched control group, a significant association between HCV infection and LPD was demonstrated only in patients with diffuse large B cell lymphoma (P = 0.007). This finding was emphasized by the observation that the HBV prevalence in the LPD group, in the control group and in the general population was almost identical.

A significant difference (P = 0.006) in the prevalence of HCV compared to HBV infection was found in patients with diffuse large B cell lymphoma. Since the prevalence of HCV and HBV infections is very similar in the general population in Israel, this finding serves as an additional indicator for a non-random association between HCV infection and diffuse large B cell lymphoma. The finding that HCV infection is associated with diffuse large B cell lymphoma is consistent with previous studies [6–9], although the association was demonstrated with other sub-classes of LPD as well [7,8,20]. However, there were no specific characteristics of lymphoma in our HCV-infected patients.

The mechanism by which HCV may initiate a monoclonal proliferation and malignancy of B cells has yet to be clarified. There is a strong association among hepatitis C, symptomatic cryoglobulinemia and low grade lymphoma [4,5]. A possible pathogenic mechanism may be chronic antigenic stimulation exerted by HCV-associated antigens, which may induce proliferation of specific B cell clones [21,22] and consequently malignant transformation. Indeed, De Re et al. [23] recently supported this hypothesis by demonstrating that the premalignant and malignant lymphoproliferations in an HCV-infected patient with essential mixed cryoglobulinemia were sequential phases of an antigen (HCV E2 protein)-driven pathologic process. Zuckerman and colleagues [24] demonstrated that HCV-infected patients – especially those with mixed cryoglobulinemia – have a higher prevalence of bcl-2 translocation and monoclonal immunoglobulin gene rearrangement than patients with chronic liver disease of other etiologies, suggesting that HCV inhibits apoptosis and induces clonal proliferation of B cells. Our study, however, supports the possible role of HCV in lymphoproliferative disorders also in patients without cryoglobulinemia.

The HCV-positive patients in our study presented with normal or slightly elevated liver enzymes without any liver-associated symptoms. This may cause a delay in the diagnosis of HCV infection in those patients. Therefore, we suggest that an anti-HCV antibody test be performed routinely in patients with diffuse large cell lymphoma. We believe that it is essential for patients with LPD, and their physician, to be aware of the presence of chronic infection with HCV for several reasons: a) these patients may receive anti-viral therapy, similar to regular HCV patients; b) they should take precautionary steps to avoid HCV transmission; and c) their family members should be encouraged to be tested for HCV.

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