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High Prevalence of Hepatitis C Virus Infection in Patients With B-Cell Lymphoproliferative Disorders in Italy

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Starting from the observation that a number of consecutive patients with non-Hodgkin's lymphoma (NHL) resulted positive for hepatitis C virus (HCV) antibodies on routine testing, we set up a survey for HCV contact prevalence in all patients with lymphoproliferative disorders (LPD) followed in our institution. We searched for HCV antibodies by a third-generation ELISA technique, followed by a confirmation test (RIBA III); serum viral RNA and HCV genotype were investigated by a RT-PCR technique. We screened a total of 315 patients suffering from B-NHL (91), multiple myeloma (56), MGUS (48), chronic lymphocytic leukemia (57), Waldentröm's macroglobulinemia (13), Hodgkin's disease (HD)(43), and T-NHL (9). While only 1 of 52 patients with a non-B-LPD (HD or T-NHL) had signs of HCV contact (i.e., 1.9%, which is in the range of the normal population in the South of Italy), 59 of 263 patients with a B-LPD (22.4%) had HCV antibodies or RNA, or both, with no major differences among the various types of disorders, except for WM, in which the rate was higher (61.5%). The same prevalence was found for patients tested at diagnosis or during the follow-up, and in transfused or never-transfused patients. Only a few patients were aware of having a liver disease; one-half of HCV-positive patients never had transaminase increase. A review of data from Central and Northern Italy is included, showing similar findings; a report from Japan has confirmed such an association, while limited surveys in England have not revealed any correlation. These findings may have important biological and clinical implications. Am. J. Hematol. 55:77–82, 1997.

Key words: hepatitis C virus; lymphoproliferative disorders; non-Hodgkin's lymphomas; multiple myeloma; Waldenström's macroglobulinemia; chronic lymphocytic leukemia

INTRODUCTION

Tests for highly contagious viral infections are now routine for patients who must undergo any surgical procedure. Such tests usually include hepatitis B virus (HBV) and human immunodeficiency virus (HIV). For reasons that are still unclear, hepatitis C virus (HCV) demonstrates uneven spreading, with some countries more affected than others. In Italy, HCV contact in the general population is estimated at 1–3% [1], with minor variations between the North and the South (1.28% vs. 1.51%) [2] and larger variations among different groups of subjects (e.g., 0.35% in blood donors, 80% in drug abusers) [3]. In a set of consecutive patients with suspected lymphoma undergoing lymph node biopsy at our hospital we found an unexpectedly high prevalence of HCV-positive status. Similar findings have been recently reported also from central [4,5] and northern [6,7] Italy. In order to quantitate this finding and to find out whether the same applies to lymphoproliferative disorders (LPD)

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other than lymphomas, we have screened for HCV all our patients suffering from an LPD and have explored correlations with a number of clinical findings. The results of this survey confirm that HCV contact has occurred much more frequently in patients with an LPD of B-cell lineage, as compared to the normal population and to patients with a non-B-LPD.

PATIENTS AND METHODS

Patients

All patients attending our institution from November 1994 to November 1995 for an LPD (new patients, those in treatment and those in post-treatment follow-up) were grouped into two categories: B-LPD and non-B-LPD. Patients suffering from multiple myeloma (MM), monoclonal gammopathy of uncertain significance (MGUS), chronic lymphocytic leukemia (CLL), Waldenström's macroglobulinemia (WM), and hairy cell leukemia (HCL) were directly included in the B-LPD group, patients with Hodgkin's disease (HD) in the non-B group. Patients with non-Hodgkin's lymphoma (NHL) were appropriately grouped only if immunological markers had proven a B- or T-cell origin. We used standard diagnostic criteria for disease classification; however, in the MGUS group, only patients with a substantial monoclonal component (MC), i.e., IgG > 1,000 mg/dl and IgA > 600 mg/dl, were considered. As for patients with an IgM MC, they were operatively classified as MGUS if the MC was 800–2000 mg/dl, and as WM if > 2,000 mg/dl. NHL were graded according to the Working Formulation [8]. The vast majority of patients were diagnosed, treated, and followed up on outpatient basis.

Control Groups

The prevalence of HCV exposure in blood donors attending our institution was obtained from the Blood Bank. In order to have a more appropriate control group, we screened 93 subjects > 40 years of age suffering from a metabolic disorder (diabetes, dyslipemia, vasculopathy), attending our hospital on an outpatient basis.

Cryoglobulins

The presence of cryoglobulins was tested qualitatively on serum obtained from blood clotted at 37°C, cooled at 4°C for 4 days. Samples containing any amount of precipitate that could be dissolved at 37°C were considered positive.

HCV Testing

Serum samples from all patients and control group were screened for HCV exposure by testing (1) anti-HCV-Ab by a third-generation enzyme-linked immunosorbent assay (ELISA) technique (EIA Seroplate, Ares-Serono or Inno-Lia III, Innogenetics, Zwijnaarde, Belgium), followed, in case of positivity, by a confirmation test with a third-generation RIBA (Chiron RIBA 3.0, Chiron Corp., Emeryville, USA); and (2) serum HCV-RNA by a polymerase chain reaction (PCR)-based technique (PCR Amplicor, Roche, Branchburg, USA). Most sera that were positive for viral RNA were also characterized for HCV genotype using a PCR-based technique (Inno-Lipa, Innogenetics). HBV markers were tested by ELISA (Radim EIA, Radim Spa, Pomezia, Italy). HCV status was defined as positive (HCV positive) when either anti-HCV antibodies or HCV-RNA, or both, had been found in the serum. No patient with overt high risk of viral infections (drug abusers, HIV-positive patients) was considered in this study. Also, LPDs developing in patients with overt cirrhosis or mixed cryoglobulinemia were excluded. HIV antibodies were checked only for patients admitting to be at risk.

Informed consent was obtained in all cases. Sixty patients were tested at diagnosis, 255 during or after treatment. Chi-square, Fisher's exact test, and Student's *t*-test were used for statistical analysis comparison, when appropriate.

TABLE I. Prevalence of HCV Contact in Our Series of Patients With an LPD and in Control Groups

	Tested	Positive[a]	%
B-LPD			
B-NHL	91	21	23.1
MM	56	9	16.1
MGUS[b]	48	11	22.9
CLL	48	8	16.7
WM[c]	13	8	61.5
HCL	7	2	28.6
Total	263	59	22.4
Non-B-LPD			
HD	43	1	2.3
T-NHL	9	0	0
Total	52	1	1.9
Control groups			
Blood donors, any age	1,568	30	1.9
Blood donors, >40 yr	500	12	2.4
Patients with a metabolic disorder, >40 yr	93	5	5.4

[a]HCV/Ab positive and/or HCV/RNA positive.
[b]With a substantial monoclonal component (MC).
[c]IgM MC >2000.
HCV, hepatitis C virus; LPD, lymphoproliferative disease; NHL, non-Hodgkin's lymphoma; MM, multiple myeloma; MGUS, monoclonal gammopathy of uncertain significance; CLL, chronic lymphocytic leukemia; WM, Waldenström's microglobulinemia; HCL, hairy cell leukemia; HD, Hodgkin's disease.

RESULTS

A total of 263 patients with a B-LPD and 52 with a non-B-LPD were screened. HCV positivity was docu-

mented in 22.4% of patients with a B-LPD and in 1.9% of patients with HD or T-NHL (Table I). The difference was highly significant ($P = 0.0016$). The male-to-female ratio was 1.2. Most positive patients (42 of 60) had both anti-HCV Ab and viral RNA in the serum; 15 patients had only Ab and 3 only RNA. A few patients were excluded from the study: two because of a previous history of cirrhosis, two because of a previous history of mixed cryoglobulinemia, one drug abuser, and two HIV positive.

In the control group, composed of diabetic, dyslipemic, or vasculopathic patients older than 40 years of age, HCV positivity was documented in 5.4% of the subjects, a prevalence that was statistically different when compared to B-LPD patients ($P = 0.0004$) and nonsignificant when compared to non-B-LPD ($P = 0.3$). In the cohort of blood donors, HCV-positive prevalence was 1.9% in the whole group and 2.4% for subjects >40 years of age; the difference was highly significant versus B-LPD patients ($P < 0.000001$) and nonsignificant versus non-B-LPD patients ($P = 0.6$).

In the set of B-LPD patients, we further analyzed possible correlations between HCV status and a number of clinical findings:

1. *Transfusions:* Of the patients who had received at least one transfusion before being tested (n = 45), 26.7% were HCV positive; in patients who had never been transfused (n = 218), the figure was 21.6% ($P = 0.60$). Thus, even patients who had never been transfused showed a high prevalence of HCV contact.

2. *Time of testing:* Forty-five patients were tested at diagnosis and 22.2% were found to be HCV positive; 218 were tested during follow-up and 22.5% were HCV positive. Thus, disease duration and type of treatment bore no relationship to HCV status.

3. *Hepatitis B exposure:* In 139 patients who were negative for HBV markers, the percentage of HCV positive was 25.2%; in 85 patients with evidence of HBV contact the percentage of HCV positive was 24.7%. Thus, no relation was found between HCV and HBV exposure, stressing the absence of a higher risk of viral infection in our HCV-positive patients. The high rate of HBV positivity in our B-LPD series (37.9%) did not differ significantly, as compared to that in the non-B group (23.9%; $P = 0.1$). These values are in the range reported previously in population screenings for adult or elderly subjects in Italy [9,10].

4. *Age:* Since the probability of HCV contact in endemic areas increases with the time of exposure, we tested for a possible correlation between age and HCV status. The mean age was 60.3 (median 62, range 15–88) for HCV-negative patients and 61.4 (median 61, range 41–88) for HCV-positive patients ($P = 0.57$). As expected, mean and median age in the group of non-B-LPD were significantly lower (35.5 and 31, respectively, range 14–77), due to the different age incidence of HD and T-NHL. In order to avoid any bias due to age difference, in the control group of patients with metabolic disorders we included only patients >40 years old, with an age distribution (mean 54.4, median 54, range 40–77) comparable to that of B-LPD patients.

5. *Transaminase elevation:* An increase of serum transaminase value (AST and/or ALT >n.v. × 2) was noticed at diagnosis or any time during follow-up in 13.4% of HCV-negative and in 50% of HCV-positive patients ($P = 0.000001$). While such a correlation was largely expected, it is noteworthy that one-half of HCV-positive patients in our series never showed increased transaminases, even on repeated testing. Liver biopsies were not performed. In HCV-positive patients, increased transaminases were found in 4 of 10 patients studied at diagnosis and in 25 of 49 studied during follow-up; thus, it is unlikely that enzyme elevation bore any relationship to chemotherapy-induced viral reactivation.

6. *NHL grading:* When NHL patients were grouped according to the Working Formulation classification, the rate of HCV positivity was 25% in low grade, 25.8% in intermediate and 18.8% in high grade. The trend in favor of low and intermediate grade did not reach statistical significance ($P = 0.77$), possibly because of the small number of patients in each subgroup.

7. *Type of immunoproliferative disorder:* The overall rate of HCV-positive status in all patients with a monoclonal component (MC) (i.e., MGUS, MM, and WM) was 52.4% in those with IgM, 24.6% in those with IgG, and 9.5% in those with IgA; a single HCV-positive patient was found among 18 patients with rarer immunoproliferative diseases (light chain disease, nonsecreting MM, solitary plasmacytoma). With one exception, all HCV-positive MM patients were in stage I.

8. *Cryoglobulins:* Patients known to have type II-mixed cryoglobulinemia who had progressed to NHL were excluded from this study. In our series, no patient had clinical signs of cryoglobulinemia. On testing, no patient had a relevant amount of serum cryoglobulins; traces or small amounts were detected in 17 of 59 HCV-positive patients (29%) (mostly in the NHL and the WM groups), and in 4 of 72 HCV-negative patients (5%). Among the patients with HD or T-NHL, 30 were tested, and none had cryoglobulins.

9. *HCV genotype:* A screening of the viral genotype was performed in 31 of 44 RNA-positive patients. We found genotype 1a in six cases, 1b in nine cases, and 2a in nine cases; genotype was unclassifiable in the remaining seven. Altered transaminases were found in all patients with genotype 1a, in 8 of 9 with genotype 1b, and in 3 of 9 with genotype 2a. No clear correlation emerged between genotype and type of LPD (Table II).

TABLE II. HCV Genotype in the Various Lymphoproliferative Disorders

	Genotype				
Disease type	1a	1b	2a	2b	Unclassifiable
NHL	3	2	4	0	1
MM	1	2	4	0	2
MGUS	1	3	0	0	2
CLL	0	2	1	0	1
WM	1	0	0	0	1

See Table I for abbreviations.

DISCUSSION

Epidemiology

We report an exceedingly high prevalence of HCV contact in all groups of patients with a B-LPD, as compared to that in the normal population of the same geographic area and to that in control groups consisting of patients with non-B-LPDs, patients with a metabolic disease, and blood donors. Using third-generation reagents for HCV testing, there was no discrepancy between ELISA and RIBA, and viral RNA was detected in most patients, thus ruling out false-positive results. Statistical analysis ruled out the possibility that the high prevalence could be attributed to previous transfusions, duration of hematological disease, or patient age. As for the latter, a bias was present in the control group of non-B-LPD (younger patients), but it could not explain the huge difference of prevalence; no bias was present in the control group of patients with a metabolic disease, since this group was age matched. Patients with a LPD evolving from liver cirrhosis or mixed cryoglobulinemia were excluded. No bias for a population having a high risk of viral infection was present in our series (drug abusers and HIV-positive patients had been excluded). An internal control was that HCV-positive patients did not show a higher prevalence of HBV contact. Only a few patients were aware of having liver disease; on testing, one-half of HCV-positive patients never exhibited abnormal transaminases. HCV infection without any sign of liver damage has been also reported in one-third of patients with mixed cryoglobulinemia [11].

The prevalence of HCV exposure in patients with a LPD was recently surveyed in other parts of Italy [4–7,12–20], in Japan [21], and in England [22–24], with variable results. As for Italy, the percentages are rather similar in southern, central, and northern Italy, with minor differences among the various disease subgroups, probably related to the small number of patients tested (Table III). In several series, the highest rate of HCV positivity is found in patients with a monoclonal IgM component (MGUS, WM). In our study as in others, the set of patients with HD or T-NHL, showing the same HCV-positive prevalence as that of the general population in Italy, constitutes a strong internal control, proving that our methodology was appropriate and that the results are specific. A HCV-positive prevalence of 17.9% in patients with monoclonal gammopathies compared to 10% of an age-matched control group was found not statistically significant in a recent report from another region from southern Italy [17], probably due to the small sample size. Results similar to ours have been recently published in Japan [21]: exposure to HCV was detected in 22% of patients with B-cell NHL and never in non-B-cell NHL and in HD. At variance, British investigators did not find increased prevalence of HCV exposure in patients with NHL in the United Kingdom [22–24].

Studying HCV genotype in our HCV–mRNA-positive patients, we did not find the prevalence of type 1b reported in Italian patients with non-post-transfusional chronic liver disease [25]. No evidence of correlation between specific genotype and type of LPD has emerged from our study, as well as from others [13]. Patients with type 2a had more often a normal transaminase level: a milder hepatic involvement by type 2a has been already noticed [26].

TABLE III. Studies on the Prevalence of Exposure to HCV in Patients With LPD in Italy

Disease type	n	%HCV+	Ref.
NHL	50	34	4
	199	28	6
	311	9	7
	150	25	12
	69	42	13
	24	21	14
	150	27	18
	126	20	19
	47	15	20
	91	23	p.r.
Total:	1,217	22	
CLL, HCL	40	5	12
	50	18	18
	29	21	20
	55	18	p.r.
Total:	174	15	
MM, MGUS	78	4	7
	90	16	12
	91	14	13
	89	14	17
	49	24	20
	104	19	p.r.
Total:	501	15	
WM	12	8	13
	6	100	15
	14	20	16
	13	23	17
	12	17	20
	13	61	p.r.
Total:	70	36	

p.r., present report; see Table I for all other abbreviations.

We think it would be desirable to carry out surveys on HCV prevalence in patients with LPDs in other countries, especially in those in which HCV infection is endemic, in order to find out whether the association we report here is a problem of a few countries or a more general phenomenon.

Role of HCV in B-Cell NHL

The strong association between exposure to HCV and B-LPDs can be explained in either of two ways: (1) patients with a B-LPD have increased risk of HCV infection, and (2) HCV-infected patients have increased risk of developing a B-LPD. Several of our findings argue against the former hypothesis: the signs of exposure to HCV have been found with the same prevalence at diagnosis and during follow-up; most LPD patients were never transfused. The latter hypothesis remains speculative, although intriguing. HCV is not only hepatotropic, but also sialotropic [27] and lymphotropic; it may be detected in hepatic lymphocytes [28], in peripheral blood mononuclear cells of infected patients [11,13,29,30] and in lymphoma tissues [31]. HCV is strongly associated with essential mixed cryoglobulinemia [32], which can be regarded as a smoldering low-grade lymphoma with a clonal B-cell expansion and a monoclonal IgM component. Even in patients with HCV-positive chronic hepatitis without cryoglobulinemia a subclinical clonal B-cell expansion has been demonstrated by molecular analysis [33]. The presence of traces of cryoglobulins in one-third of our HCV-positive patients is also intriguing; as these patients have overt LPD and no clinical signs of cryoglobulinemia, it is unlikely that all of them had had subclinical cryoglobulinemia subsequently progressing to LPD. We think that the biological relevance of the presence of cryoglobulins should not be overestimated: it is not a marker of a different disease, rather, it could be simply another sign of exposure to HCV.

If HCV is indeed causative of lymphoid malignancies, it could do so either by acting directly (i.e., producing an early hit in a sequence of oncogenic events), or indirectly (i.e., by causing expansion of lymphoid clones that may subsequently undergo mutational events). In addition, interactions with other undiscovered or unknown viruses (''passenger viruses'') cannot be ruled out. Other examples of HCV involvement in oncogenesis do exist: hepatic carcinoma often develops in patients with HCV-positive chronic hepatitis [34]. HCV has been also incriminated as a trigger of autoimmunity [20,35], and autoimmune disorders may predispose to NHL. Finally, there are a few examples of lymphoproliferative disorders not only caused but also maintained by infectious agents: Epstein-Barr virus (EBV)-induced lymphomas in transplanted patients [36] and *Helicobacter pylori*-related gastric MALT lymphomas [37]. Two very recent reports from other parts of Italy [19,38] have stressed the high prevalence of HCV-positive in patients with MALT lymphoma (36.4% and 50%, respectively). It would be interesting to verify whether some kind of antiviral therapy is of any benefit for the subset of HCV-positive LPD patients. We have preliminary unpublished results of a higher response rate to interferon-α (IFN-α) in the subgroup of HCV-positive Waldenström's macroglobulinemia patients.

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NOTE ADDED IN PROOFS.

A high juvalence of HCV positivity has been recently reported also for patient suffering from B-NHL in USA (Zuckerman et al, Blood 88 (suppl. 1), 1996, Abst 877.

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