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Prevalence of hepatitis C virus infection in lymphoproliferative diseases other than B-cell non-Hodgkin's lymphoma, and in myeloproliferative diseases: an Italian multi-center case-control study

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A B S T R A C T

Background and Objectives. Infection with hepatitis C virus (HCV) is associated with type II mixed cryoglobulinemia (MC), a lymphoproliferative disorder which, in some patients, evolves into overt B-cell non-Hodgkin's lymphoma (B-NHL). Recently, the association between HCV infection and B-NHL, which had long been controversial, was confirmed in a large case-control study. Little knowledge is, however, available on possible associations between HCV infection and other lymphoid or myeloid malignancies. The present study was set up in order to investigate this aspect.

Design and Methods. The study was conducted in hematology departments of ten hospitals in different Italian cities. The cases consisted of consecutive patients with a new diagnosis of T-NHL, Hodgkin's disease (HD), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), multiple myeloma (MM), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). The controls were patients in other departments of the same hospitals. HCV infection was investigated by testing for HCV antibodies and HCV-RNA in serum samples.

Results. The prevalence of HCV infection was not higher in patients with HD (3.2%, 5 out of 157 cases) or MM (4.7%, 5 out of 107) than in controls. On the other hand, it was consistently higher in T-NHL (13.8%, 4 out of 30), CLL (9.0%, 9 out of 100), ALL (7.6%, 5 out of 54), AML (7.9%, 11 out of 140), and CML (12.2%, 6 out of 49) patients. These patient groups were not, however, large enough to render the results statistically significant.

Interpretation and Conclusions. Our data suggest that HCV infection may be associated not only with B-NHL but also with some other lymphoid and myeloid malignancies.

Key words: hepatitis C virus, HCV, lymphoproliferative diseases, myeloproliferative diseases

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Hepatitis C virus (HCV) is the major etiological agent of post-transfusion and sporadic non-A, non-B chronic hepatitis and one of the most important causes of chronic liver diseases.[1,2] It has also been associated with extrahepatic diseases[3] and, indeed, an association between chronic HCV infection and type II mixed cryoglobulinemia (MC), a systemic immune complex-mediated disorder, has been firmly established.[4] Type II MC is characterized by clonal expansion of B cells and can be considered a smoldering, low-grade lymphoma that may evolve into an overt or high-grade lymphoma in some patients.[5] This knowledge has prompted investigations on whether there is also an association between HCV infection and B-cell lymphomas. A large number of studies have generated conflicting results on this issue, a positive association being found in some of the studies,[6-18] but not in others.[19-25]

Our own group recently conducted a large case-control study to investigate a possible association between HCV infection and B cell non-Hodgkin's lymphoma (B-NHL).[26] We found that B-NHL patients were 3.1 times more likely to be infected with HCV than controls, thereby confirming a positive association. In contrast to these many studies on B-NHL, there is little information on a possible association between HCV infection and other lymphoid or myeloid malignancies. We have conducted the present study in an effort to clarify this aspect. We investigated the prevalence of HCV infection in patients with a new diagnosis of T-NHL, Hodgkin's disease (HD), multiple myeloma (MM), chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), and chronic myeloid leukemia (CML). Controls were patients in non-hematology departments of the same hospitals.

Design and Methods

Cases and controls

The study population consisted of adults (i.e., 15 years or older) admitted to ten hospitals in different cities located throughout Italy [Bari, Bergamo, Montefiascone, Naples, Palermo, Reggio Calabria, Rome (2 hospitals), San Giovanni Rotondo, and Sassari] from January 1998 through to February 2001. Cases had been consecutively admitted to the hematology wards of the study hospitals with a new diagnosis of T-NHL, HD, CLL, ALL, MM, AML or CML and had not received anti-cancer treatment. All participating hematology departments are part of the Italian Cooperative Group for the Study of Hematologic Diseases in Adults (GIMEMA).

T-NHL and HD were diagnosed based on the results of a lymph node biopsy. The stage of T-NHL and HD at diagnosis was determined for all patients. The type and stage of T-NHL were defined according to the REAL/WHO classification.[27,28]

The diagnosis of acute and chronic leukemias was based on characterization of the leukemic cells, obtained from bone marrow and/or peripheral blood, by cytochemical staining, immunophenotyping, cytogenetics and molecular biology studies when appropriate. The criteria established by the WHO classification were those considered for the diagnosis. MM was diagnosed by serum and urine protein analysis, bone marrow aspirate/biopsy, and skeletal survey.

The control group consisted of patients in other departments of the same hospitals, specifically, the departments of dentistry, dermatology, general surgery, gynecology, internal medicine, ophthalmology, orthopedics, otorhinolaryngology, and traumatology. As for the cases, only control patients with a newly diagnosed disease were included. Eligible control patients were identified once a week, throughout the duration of the study and consecutively enrolled by the local investigator in one or more of the departments listed above. Written informed consent was obtained from all study participants.

Data collection

In each hospital, both cases and controls were interviewed by the same, specifically trained, physician using a standardized questionnaire which consisted of three sections: 1) social-demographic characteristics; 2) medical history; and 3) history of behavioral and environmental exposure, including occupational exposure. Interviewing physicians were aware which patients were cases and which were controls, but were unaware of the study hypothesis. Cases and controls were interviewed within one week of hospital admission.

HCV antibody and viral assays

Serum samples were collected from both cases and controls at hospital admission and sent to the Laboratory of Virology at the Istituto Superiore di Sanità (National Health Institute of Italy, Rome), where they were stored at –80°C until testing. Testing for HCV was performed in one batch (i.e., once all of the samples had been collected) and in the same laboratory. HCV antibodies were detected using an enzyme immunoassay (EIA-3; Ortho HCV 3rd generation; Ortho Diagnostic Systems, Raritan, New Hampshire, USA). HCV immunoreactivity was confirmed with a third generation immunoblot assay (Riba-3, Chiron Corporation, Emeryville, California, USA, and Ortho Diagnostic Systems). Moreover, HCV-RNA was determined in all cases, in all anti-HCV-positive controls and in a randomly chosen 10 percent sample of anti-HCV-negative controls (Cobas Amplicor 2.0, Roche Diagnostic Systems, Branchburg, New Jersey, USA). Genotyping was performed by an Innogenetics Line Probe assay (Innogenetics, Zwijndrecht, Belgium). For the purposes of this analysis, patients were considered as HCV-positive if they had antibodies to HCV and/or if HCV-RNA was detected.

Data analysis

Adjusted odds ratios (OR) and corresponding 95% confidence intervals (CI) were computed overall and by gender by means of unconditional multiple logistic regression including age (both as a categorical variable, in ten-year groups, and as a continuous variable), level of education, and place of birth. Furthermore, to determine whether the inclusion of cases and controls with a history of blood transfusion, intravenous drug use, and previous surgical interventions could have biased the OR estimates, we determined the distribution of these factors among cases and controls and adjusted for those factors whose distribution varied between the two groups.

Results

The study population consisted of 30 persons diagnosed with T-NHL, 157 with HD, 100 with CLL, 54 with ALL, 107 with MM, 140 with AML, 49 with CML, and 396 controls. The hospital departments in which the controls were recruited were as follows: internal medicine (26.3% of controls); ophthalmology (24.5%); general surgery (13.9%); dermatology (11.9%); orthopedics (7.1%); and other departments (16.4%). The most frequent diagnoses were: retinal detachment and cataracts (19%); renal calculi (14%); thrombophlebitis, cardiomyopathy, hypertension or hypercholesterolemia (13%); atopic dermatitis or urticarial eruptions (7%); and trauma (5%).

Table 1 shows the prevalence of HCV infection by gender and age for both cases and controls. Four of 30 (13.8%) cases with T-NHL were HCV-positive, as were 5 of 157 (3.2%) with HD, 9 of 100 (9.0%) with CLL, 4 of 54 (7.6%) with ALL, 5 of 107 (4.7%) with MM, 11 of 140 (7.9%) with AML, 6 of 49 (12.2%) with CML, and 22 of 396 (5.6%) controls. The 66 cases or controls who were considered HCV-positive were all positive for HCV antibodies by both enzymic and immunoblot assays; 55 of them were also positive for HCV RNA. The overall prevalence among cases of T-NHL, CLL, ALL, AML, and CML was higher than among controls, whereas this difference was not found for HD and MM. As expected, the prevalence increased with age for both cases and controls.

Table 2 indicates the adjusted ORs for cases and controls, both overall and broken down by gender. When comparing the prevalence in cases and controls, and adjusting for possible confounding factors, the adjusted, overall ORs were 2.2 (95% CI 0.65-7.6) for T-NHL, 1.2 (95% CI 0.61-3.3) for HD, 1.3 (95% CI 0.56-2.9) for CLL, 2.4 (95% CI 0.81-7.1) for ALL, 0.6 (95% CI 0.23-1.8) for MM, 1.3 (95% CI 0.62-2.9) for AML, and 2.3 (95% CI 0.84-6.4) for CML. As to the ORs broken down by gender, for some diseases (e.g. CLL and AML) there were considerable differences between males and females. These values were obviously calculated on smaller numbers of patients and, therefore, it is difficult to draw firm conclusions from the results. Nevertheless, they may serve as useful indicators for future studies on larger populations of patients.

With regard to other possible confounding variables, 6 (0.9%) of the 638 cases and 11 (2.7%) of the 396 controls reported intravenous drug use, and 64 (10.1%) of the cases and 31 (7.9%) of the controls reported having received blood transfusions. When adjusting for these variables, the ORs differed only slightly from those reported above (*data not shown*). The proportion of cases who had undergone surgery (65%, range 50-77%) was very similar to that among controls (64%); so we did not adjust for this variable.

Table 3 shows that the distribution of HCV genotypes was similar among HCV-positive cases and controls, the genotypes most commonly found being 1b and 2a/2c.

Discussion

In this report we present the results of a study aimed at investigating a possible association between infection with HCV and lymphoid and myeloid malignancies other than B-NHL, i.e. T-NHL, HD, CLL, ALL, MM, AML, and CML. This study is part of a large case-control study that has brought further evidence in favor of a positive association between HCV infection and B-NHL.[26]

Before discussing the results, it is important to point out that we took great care to avoid selection biases in this study. First, the controls were recruited in different departments of the same hospitals as the cases, and they included a broad range of patients with different, newly diagnosed diseases unrelated to HCV infection. The prevalence of HCV among controls (5.6%) was similar to that expected in a general population of comparable age-group distribution and geographic area (range 4.85-8.33%). Moreover, we adjusted the ORs for age, sex, level of education, and place of birth, and we also evaluated other possible confounders (i.e. history of intravenous drug use, blood transfusion, chronic illness and surgery).

The results show that the prevalence rates of HCV infection in patients with HD and MM were not higher than those in controls (3.2% and 4.7% for HD and MM, respectively). In consideration of the relatively large number of patients tested in these two case populations, it is reasonable to draw the conclusion that no association exists between HCV infection and HD or MM, although the confidence intervals do not completely exclude this possibility.

As regards the other malignancies studied, we found higher rates of HCV infection in the cases than in the controls: 13.8% in T-NHL, 9.0% in CLL, 7.6% in ALL, 7.9% in AML, and 12.2% in CML. As to the adjusted ORs, these were considerably higher for T-NHL, ALL and CML cases than for controls. The groups of patients were not, however, large enough to allow these differences to be statistically significant. Therefore, further studies with larger populations of patients are needed to confirm the possibility of such an association.

Some previous studies had already investigated prevalence rates of HCV infection in similar populations. For example, in a prospective study in France,[25] the prevalence of HCV infection was investigated in a group of patients with various hematologic diseases. For most of the malignancies considered (B-NHL, HD, CLL, MM, Waldenström's macroglobulinemia, and myeloproliferative diseases) no positive association was found. A higher prevalence rate was found in patients with ALL and hairy cell leukemia (HCL) than in controls, but the number of patients studied for each of these diseases was so small (n = 6 and 17 for HCL and ALL, respectively) that no conclusions could be drawn. As to the other malignancies, results for B-NHL, CLL, and myeloproliferative diseases contrast with those that we obtained in our previous study in B-NHL patients[26] and in the present study in ALL and in CML patients. Discrepant results on a positive association between HCV infection and B-NHL have been repeatedly reported in the past depending on the geographic area where the studies were performed,[6-18] suggesting a possible contribution of other etiological factors (e.g. environmen-

Table 1. HCV prevalence by gender and age among patients with T-NHL, HD, CLL, ALL, MM, AML, CML, and controls; Italy, 1998-2001.

	Controls			*Cases of T-NHL*		
	No.	*No. of HCV -positive*	*% of HCV -positive*	*No.*	*No. of HCV -positive*	*% of HCV -positive*
Sex						
Male	205	15	7.3	26	4	16
Female	191	7	3.6	4	0	0
Age (years)						
15-35	103	0	0	6	0	0
36-55	128	6	4.7	6	0	0
56-75	125	10	8	15	2	14.3
≥ 76	40	6	15	3	2	66.7
Total	396	22	5.6	30	4	13.8
	Cases of HD			*Cases of CLL*		
Sex						
Male	100	4	4	67	5	7.5
Female	57	1	1.8	33	4	12.1
Age (years)						
15-35	82	0	0	1	0	0
36-55	48	3	6.3	19	0	0
56-75	25	2	8	67	6	9
≥ 76	2	0	0	13	3	23.1
Total	157	5	3.2	100	9	9
	Cases of ALL			*Cases of MM*		
Sex						
Male	30	3	10.3	53	1	1.9
Female	24	1	4.2	54	4	7.4
Age (years)						
15-35	21	1	5	2	0	0
36-55	15	1	6.7	17	0	0
56-75	14	2	14.3	80	4	5
≥ 76	4	0	0	8	1	12.5
Total	54	5	7.6	107	5	4.7
	Cases of AML			*Cases of CML*		
Sex						
Male	79	8	10.1	29	4	13.8
Female	61	3	4.9	20	2	10
Age (years)						
15-35	24	0	0	9	0	0
36-55	24	1	4.2	9	0	0
56-75	66	6	9.1	24	4	16.7
≥ 76	26	4	15.4	7	2	28.6
Total	140	11	7.9	49	6	12.2

Table 2. Association between HCV and T-NHL, HD, CLL, ALL, MM, AML, CML; adjusted ORs: overall and by gender. Italy, 1998-2001.

Gender	*Overall Adjusted OR* (95% CI)*	*Male Adjusted OR* (95% CI)*	*Female Adjusted OR* (95% CI)*
Controls	1	1	1
T-NHL	2.2 (0.6-7.6)	2.2 (0.6-7.8)	ND°
HD	1.2 (0.6-3.3)	1.2 (0.4-4.2)	1.2 (0.1-10.9)
CLL	1.3 (0.56-2.9)	0.7 (0.2-2.2)	2.3 (0.6-9.4)
ALL	2.4 (0.81-7.1)	2.6 (0.6-10.9)	0.8 (0.08-8.5)
MM	0.6 (0.23-1.8)	0.2 (0.02-1.4)	1.5 (0.4-6.0)
AML	1.3 (0.62-2.9)	1.4 (0.5-3.6)	0.7 (0.1-3.1)
CML	2.3 (0.84-6.4)	1.9 (0.6-6.7)	2.8 (0.5-17.5)

**Adjusted by age (continuous), level of education, and place of birth.*
°ND: not determined.

tal, genetic, infectious) to neoplastic transformation.

In another study, the prevalence of HCV infection was investigated in Japanese NHL patients.[29] A positive association was found with B-NHL, but not with T-NHL. This latter result contrasts with our present observation. However, in both studies, our own and that of Imai *et al.*, the investigated patient populations were so small (n = 29 in our study and 31 in that of Imai *et al.* that it is difficult to draw conclusions. Significantly larger patient populations are needed for this purpose, a difficult undertaking for this rare lymphoproliferative disease. Our data tend to exclude a positive association between HCV infection and HD or MM, although the confidence intervals do not completely exclude this possibility. On the other hand, adjusted ORs for T-NHL, ALL, and CML, while not being statistically significantly different from those for controls, nevertheless suggest the possibility of a positive association. Confirmation of such an association on larger patient populations would be of particular interest for ALL and CML in view of clarifying the pathogenic mechanism(s) whereby HCV infection might contribute to neoplastic transformation. As regards B-NHL, two such mechanisms have been put forward to explain the contribution of HCV infection to neoplastic transformation.

The first, which does not imply, necessarily, direct infection of target cells, presumes that a key event is chronic antigenic stimulation of B cells by HCV proteins, in particular the HCV-E2 protein.[30] In fact, immunoglobulin variable region genes expressed by B-NHL cells from HCV-positive patients have been shown to exhibit features of ongoing somatic mutations,[31] indicative of antigen selection, as well as the use of a restricted set of variable region genes,[31] indicative of the presence of a common antigen. Further findings suggest that HCV-associated lymphomas may originate from B cells that were initially activated by the HCV-E2 protein.[32] Moreover, the histologic presentation of many B-NHL cells from HCV-positive patients is typical of germinal center (GC) and post-GC B cells,[33] again suggesting that lymphomagenesis occurs when B cells proliferate in response to an antigen. The second proposed mechanism hypothesizes HCV infection of the target cells that eventually undergo transformation. In favor of this mechanism are studies that have reported the presence of HCV sequences in lymph node biopsies from patients with B-NHL[11] and of HCV-associated proteins within lymphoma cells.[9] Moreover, studies in severe combined immunodeficiency mice[34] have provided evidence of persistence and low-rate multiplication of HCV in human mononuclear cells. A recent report describing the establishment of a B-cell line from an HCV-infected B-NHL patient is consistent with these observations.[35] HCV RNA and proteins were detectable and HCV virions are continuously produced by this cell line in culture. In addition, a line of transgenic mice that express the HCV transgene has been found to develop malignant lymphoma with a high frequency over the ages of 20 months.[36] HCV core mRNA was found in the enlarged lymph nodes of these animals. Since these mice should have been tolerant to the transgenic pro-

Table 3. Distribution of HCV genotypes among patients with T-NHL, HD, CLL, ALL, MM, AML, CML (cases) and controls; Italy, 1998-2001.

HCV genotype	*Controls*	*T-NHL*	*HD*	*CLL*	*ALL*	*MM*	*AML*	*CML*
1a	1	0	0	0	0	0	1	0
1b	8	3	2	3	2	2	0	1
2a/2c	7	0	2	6	2	2	6	3
3a	0	0	1	0	0	0	0	0
4c/4d	0	0	0	0	0	0	0	1
Unknown	0	1	0	0	0	0	1	0
Total	16	4	5	9	4	4	8	5

tein, this observation can be considered as another piece of evidence in support of direct infection of target cells as a crucial event in contributing to neoplastic transformation.

While these two mechanisms are not mutually exclusive, it would be of considerable interest to discriminate between the two possibilities. In this regard, our results on a possible association between HCV infection, ALL and CML, are of particular note. In fact, ALL cells resemble precursor B cells, without showing any evidence of somatic mutations,[37] while CML cells derive from a lineage that is unresponsive to specific antigen recognition events. Confirmation of the present finding in more patients would exclude, in both of these diseases, any possible contribution of chronic antigenic stimulation as a mechanism contributing to neoplastic transformation and would favor direct infection of target cells as the key event in this transformation.

Contributions: AP and AM designed the study; EB, FMa and AP wrote the manuscript; RC was responsible for the statistical analysis; MR was responsible of the centralized blood tests; SF and FM supervised the study; PM, MGS, EI, ADR, BM, GS, MM, AMB, RN, LP represented the single centers contributing to the study; all tables were created by RC. The authors thanks Valeria Wenzel (Istituto Superiore di Sanità) for editing the paper. The authors reported no conflict of interest.

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