letter to the editor
Haematologica 1995; 80:486-487

HIGH PREVALENCE OF ANTIBODIES TO HEPATITIS C VIRUS IN PATIENTS WITH LYMPHOPROLIFERATIVE DISORDERS

Luigi Cavanna*, Giorgio Sbolli*, Elisabetta Tanzi°, Luisa Romanò°, Giuseppe Civardi*, Elisabetta Buscarini#, Daniele Vallisa*, Raffaella Berté*, Agostino Rossi@

**First Department of Internal Medicine, Hematology Section, Hospital of Piacenza; °Institute of Virology, University of Milan; #Division of Gastroenterology, Hospital of Piacenza; @Transfusion Center, Hospital of Piacenza, Italy.*

Sir,

data about hepatitis C virus (HCV) infection in patients with hematologic malignancies are fragmentary and poor,[1-4] and concern patients who were previously treated (chemotherapy and/or transfusion) for their disease. Angelucci recently confirmed in this journal[5] that HCV infection is one of the major clinical problems of patients with thalassemia who began transfusional therapy before HCV screening tests became available. To our knowledge, the prevalence of HCV antibodies performed at the onset of disease in patients with hematologic malignancies has never been reported in the literature.

Zignego *et al.*[6] and Bartolomé *et al.*[7] demonstrated that HCV is able to infect mononuclear blood cells; in addition, a role for HCV infection in the pathogenesis of Waldenström's macroglobulinemia and type II cryoglobulinemia has been suggested by Santini *et al.*[8] and by Agnello *et al.*[9] Recently, Ferri *et al.*[10] reported a high prevalence of HCV infection in a series of 50 patients with non-Hodgkin's lymphoma (NHL).

These data prompted us to investigate retrospectively the prevalence of HCV antibodies among the 300 patients with lymphoproliferative disorders who were admitted to our Hematology Department between 1985 and 1990.

The population studied included 170 patients with malignant lymphomas (150 NHL and 20 Hodgkin's disease [HD]), 90 with plasma cell dyscrasias (PCD), 40 with chronic lymphocytic leukemia CLL). At admission only two patients presented a previous history of blood product transfusions or jaundice. Liver function tests were investigated in all these patients at diagnosis. All sera (collected at diagnosis, frozen and stored at –40°C) were tested for anti-HCV antibodies using a commercial enzyme linked immunosorbent assay (Ortho HCV Elisa test System, second genaration, Raritan, NJ). The methods and evaluation of results were performed according to the manufacturer's instructions. In order to define the specificity of the results obtained by Elisa, reactive sera were also investigated by a second-generation (four-antigen) recombinant immunobinding assay (RIBA 2, Chiron Corp., Emeryville, CA) and Ortho Diagnostic System. Sera were classified as positive, negative and indeterminate on the RIBA assay according to manufacturer's criteria. The prevalence of anti-HCV in the 300 patients with lymphoproliferative disorders was compared with a control group of 3,108 blood donors (matched for age and sex), coming to our hospital's Transfusion Center. For statistical analysis we used Fisher's exact test and the chi-square test. The prevalence of HCV antibodies in the 300 patients with lymphoproliferative disorders are summarized in Table 1. At diagnosis fifty-seven (19.7%) of these patients showed anti-HCV antibodies, 226 (75%) were non reactive and 17 (5.6%) were indeterminate. The prevalence of anti-HCV antibodies in this cohort of patients was therefore 19.7%; the prevalence of anti-HCV positivity was 1.7% in the control group, ($p<0.001$). Liver tests showed increased transaminases at diagnosis in 12/57 (21%) anti-HCV-positive and in 11/226 (4.8%) anti-HCV-negative patients.

In sumamry, this study revealed a high preva-

Correspondence: Luigi Cavanna MD, 1st Internal Medicine, Hematology Section, Hospital of Piacenza, via Taverna 49, 29100 Piacenza, Italy. Tel. international +39.523.302285. Fax international +39.523.302328.
Acknowledgements: This work was supported in part by "Associazione Piacentina per lo Studio delle Leucemie e delle altre Malattie del Sangue".

Table 1. Prevalence of serum HCV antibodies in 300 in lymphoproliferative disorders.

Anti-HCV	*NHL*	*HD*	*PCD*	*CLL*
Pos 57 (19.7%)	38 (25%)	2 (10%)	15 (16%)	2 (5%)
Neg 226 (75%)	99 (66%)	17 (85%)	72 (80%)	38 (95%)
Ind 17 (5.6%)	1 (5%)	3 (3%)	0	
Tot 300	150	20	90	40

NHL: non-Hodgkin's lymphoma; HD: Hodgkin's disease; PCD: plasma cell dyscrasias; CLL: chronic lymphocytic leukemia; Pos: positive; Neg: negative; Ind: indeterminate

lence of anti-HCV antibodies (19.7%) among patients with lymphoproliferative disorders as compared with the control group of healthy blood donors (1.7%). We can exclude the idea of false positive results suggested by some authors[2] since all the cases in our study reported as positive were confirmed by the RIBA test. Recently, Zignego *et al.*[6] demonstrated that HCV infects blood mononuclear cells, that viral replication probably occurs in these cells, and that HCV can be found in T and B lymphocytes. These data are very interesting and may suggest that HCV could perhaps play a role in the pathogenesis of lymphoproliferative disorders. In fact, since HCV primarily infects hepatocytes, it is now well documented that there is a strong association between HCV infection and the development of hepatocellular carcinoma (HCC). However, the presence of cirrhosis in most cases of HCV-related HCC may indicate an indirect role for HCV in carcinogenesis.

Recently, a high prevalence of HCV infection was reported in two small groups of patients with Waldenström's macroglobulinemia[8] and type II cryoglobulinemia.[9] These authors postulate a role for HCV in the pathogenesis of these two conditions. Persistence of HCV in the immune system could also play a role, either directly or indirectly, in the pathogenesis of lymphoproliferative disorders.[8] While far from being conclusive in this matter, our results demonstrate that the prevalence of anti-HCV antibodies was very high in 300 patients with lymphoproliferative disorders at diagnosis. It must be emphasized that in our study polymerase chain reaction (PCR) was not employed to detect HCV-RNA, and therefore the prevalence of HCV infection may be underestimated in our patients group. Moreover, Zaaijer *et al.*[11] in their study on the reliability of HCV-PCR revealed that only 16% of participating laboratories performed this technique faultlessly. Therefore even studies that made use of PCR may not be trustworthy.

In conclusion, we believe that our study the need to investigate HCV infection in patients with lymphoproliferative disorders. The findings presented here, if confirmed in a larger number of patients, could also provide a basis for studying the hypothetical role of HCV in the pathogenesis of lymphoproliferative disorders.

References

1. Murphy MF, Waters AH, Grint PCA, Hardiman AE, Lister TA. Hepatitis C infection in multitransfused patients with acute leukemia. Lancet 1990; 335:58-9.
2. Boudard D, Lucas JC, Muller JY, Le Carrer D, Planchon B, Harousseau JL. False-positive hepatitis C virus antibody tests in paraproteinaemia. Lancet 1990; 336:63.
3. Brink NS, Chopra R, Perrons CJ, et al. Acute hepatitis C infection in patients undergoing therapy for haematological malignancies: a clinical and virologic study. Br J Haematol 1993; 83:498-503.
4. Locasciulli A, Cavalletto D, Pontisso P, et al. Hepatitis C virus serum markers and liver disease in children with leukemia during and after chemotherapy. Blood 1993; 82:2564-7.
5. Angelucci E. Antibodies to hepatitis C virus in thalassemia. Haematologica 1994; 79:353-5.
6. Zignego AL, Macchia D, Monti M, et al. Infection of peripheral mononuclear blood cells by hepatitis C virus. J Hepatol 1992; 15:382-6.
7. Bartolomé J, Castillo I, Quiroga JA, Navas S, Carreno V. Detection of hepatitis C virus RNA in serum and peripheral blood mononuclear cells. J Hepatol 1993; 17:90-3.
8. Santini GF, Crovatto M, Modolo ML, et al. Waldenström macroglobulinemia: a role of HCV infection? Blood 1993; 82: 2932.
9. Agnello V, Chung TR, Kaplan LM. A role for hepatitis C virus infection in type II cryoglobulinemia. N Engl J Med 1992; 327:1490-5.
10. Ferri C, Caracciolo F, Zignego AL, et al. Hepatitis C virus infection in patients with non-Hodgkin's lymphoma. Br J Haematol 1994; 88:392-4.
11. Zaajer HL, Cuypers HTM, Reesink HW, Winkel IN, Gerken G, Lelie PN. Reliability of polymerase chain reaction for detection of hepatitis C virus. Lancet 1993; 341:722-4.