

HEPATIS C VIRUS: A LINKAGE BETWEEN HEMATOLOGY AND HEPATOLOGY ESTABLISHED THROUGH MAJOR CONTRIBUTIONS BY ITALIAN RESEARCH

In this issue of *Haematologica*, Luppi and Torelli analyze the pathogenetic role of some lymphotropic viruses in human lymphoproliferative disorders.¹ This has been a field of active research in the last few years, and we should be proud of the fact that important investigations on the relationship between hepatitis C virus (HCV) and lymphoproliferative disorders have been performed in Italy. In addition, Torelli and coworkers have made important contributions to studies on herpesviruses.

The close association between HCV infection and mixed cryoglobulinemia (MC) represented the first evidence that this virus may have an etiopathogenetic role in lymphoproliferative disorders. Ferri *et al.*² investigated the prevalence of HCV infection of peripheral blood mononuclear cells in a series of 16 patients with type II mixed cryoglobulinemia. Previous exposure to HCV was shown in all cases (100%); moreover, HCV RNA was detected in peripheral lymphocytes from 13 out of the 16 patients, whereas it was never found in mononuclear blood cells from 20 control subjects. These findings strongly suggested that HCV infection might be responsible for the clonal B-cell expansion underlying the systemic manifestations of MC.

Pozzato *et al.*³ studied the clinical, histologic, and virologic findings of 31 patients affected with mixed cryoglobulinemia. The prevalence of anti-HCV antibodies was high (84%); polymerase chain reaction amplification of the 5' untranslated region of HCV was positive in 84% of subjects, and core region amplification was positive in 96%. A high prevalence of genotype II was found (77%), and chronic liver disease was present in 48% of patients. Bone marrow biopsy specimens showed the presence of low-grade non-Hodgkin's lymphomas in 12 cases (39%), whereas infiltration appeared to be reactive rather than monoclonal in 11 patients. This study confirmed that mixed cryoglobulinemia is closely associated with HCV infection since only

one patient was apparently not infected by the virus, and suggested that this disease is associated with a high prevalence of low-grade non-Hodgkin's lymphomas (NHLs).

The same authors investigated the long-term effects of α -interferon on clinical, hematological and virological parameters in a group of 18 patients affected with type II mixed cryoglobulinemia.⁴ A bone marrow biopsy was performed in all patients, and a liver biopsy was obtained in those with biochemical signs of chronic liver disease. All patients followed the same treatment schedule: three million units of recombinant interferon- α s.c., three times a week for 1 year. In 5 cases bone marrow histology showed the presence of a monoclonal lymphocytic infiltrate. Liver biopsies were performed in 13 (72%) of the patients and chronic liver disease was found in all 13. Anti-HCV antibodies were present in 17 (95%) subjects. HCV-RNA was detected in all cases (100%) before therapy. Five (28%) patients achieved a complete response and 9 (50%) a partial response, while the others (4 cases, 22%) showed minor responses. Four patients cleared the virus and obtained a complete remission of the MC. This study confirmed that HCV may be a cause of mixed cryoglobulinemia and suggested that α -interferon may be an effective agent for the treatment of this disorder.

At this point Ferri *et al.* decided to investigate HCV infection in a series of 50 unselected Italian patients with B-cell NHL.⁵ Antibodies against HCV were found in 30% of NHL, and HCV viremia in 32% of cases. HCV-related markers were detected in 34% (17/50) of NHL patients; this prevalence is particularly significant when compared with HCV seropositivity in Hodgkin's disease (3%) and healthy controls (1.3%). These data have been confirmed by Cavanna *et al.*⁶

Franzin *et al.*⁷ investigated clonal expansions of IgM-producing B cells in 38 patients with a

chronic hepatitis C virus infection. Eight patients were affected with type II mixed cryoglobulinemia (two of whom also suffered from non-Hodgkin's lymphoma and one from Waldenström's disease), one with type III mixed cryoglobulinemia, one with Waldenström's disease, and 28 with chronic liver disease. Clonal Ig gene rearrangements were detected in all patients with type II mixed cryoglobulinemia, as well as at a high frequency (24%) in the HCV-infected patients without cryoglobulinemia. A polyclonal pattern was present in the patient with type III mixed cryoglobulinemia and in the 15 normal individuals and 16 age-related patients with HCV-negative alcoholic liver disease investigated as controls. The serum levels of rheumatoid factor were increased in all patients with a clonal expansion, suggesting that the expanded B-cell clones belong to the rheumatoid factor-producing B-cell subset.

De Vita *et al.* have reported for the first time localization of HCV within a parotid non-Hodgkin's lymphoma (NHL) lesion in the course of HCV-related type II essential MC, an important step toward implicating this agent in lymphomagenesis.⁸ Plus and minus strand HCV RNA was first demonstrated by polymerase chain reaction on complete RNA from the lesion. Sialotropic viruses already shown to be involved in lymphoproliferation, ie Epstein-Barr virus and human herpesvirus-6, were absent from the same tissue lesion. According to the

current models of B-cell lymphomagenesis, a role for HCV as an exogenous antigenic stimulus should be considered for NHL development in the present case, whereas malignant B cells do not seem to permit active HCV replication.

These are just a few examples of the major contributions made by Italian science toward defining the pathogenetic role of HCV in lymphoproliferative disorders. The reader is referred to the review by Luppi and Torelli¹ for details.

References

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