Hepatitis C Virus and Lymphoproliferative Disorders

To the Editor:

Following our previous study on the association between hepatitis C virus (HCV) infection and idiopathic B-cell non-Hodgkin's lymphomas (NHL), Silvestri et al investigated the prevalence of this virus in a large series of lymphoproliferative disorders, including B-cell malignancies. On the whole, an increased prevalence (9%) of anti-HCV antibodies was detected in patients with B-cell NHL; the relative risk of being infected by HCV was significantly higher in this group of lymphomas than that of general population. Moreover, the analysis of HCV infection among different histological subgroups suggested that a strong association was present only with the immunocytomas (30%), which are invariably associated with mixed cryoglobulinemia (MC). This study confirms, in part, the results of our previous research showing the presence of HCV infection in one-third of idiopathic B-cell NHL, regardless their different grades of malignancy. We found the same findings in a larger patients' series (Table 1); in addition, in patients with B-cell NHL not associated with MC, Luppi et al reported the presence of anti-HCV antibodies and HCV RNA in 42% and 30% of sera and pathologic lymph nodes, respectively. More recently, a surprisingly high prevalence (50%) of HCV infection has been documented in low-grade MALT lymphoma. A careful analysis of the above studies suggests that some differences could be, at least in part, explained by different methodological approaches. In particular, the higher prevalence (32% v 9%) of HCV infection in our B-cell NHL, classified according to the Working Formulation, can partially be related to the exclusion of some patients' subsets such as chronic lymphocytic leukemia (CLL) or hairy cell leukemia, which seem to be less frequently associated with HCV infection. Moreover, the sole correlation between HCV and immunocytomas, reported by Silvestri et al, was the result of the exclusion from statistical analysis of 2 of 5 anti-HCV antibody-positive patients with centroblastic-centrocytic follicular + diffuse lymphomas because of the absence of serum HCV RNA and of 2 of 5 HCV RNA-positive centroblastic lymphomas because of their previous history of MC. In anti-HCV-seropositive individuals, the lack of HCV viremia cannot exclude the presence of viral genome in other tissues; we previously showed that, in MC patients, the prevalence of HCV RNA increased from 50% to 81% when detected in the sera and in peripheral lymphocytes, respectively. The tropism of HCV for lymphatic tissues has been largely demonstrated: the infection of lymphocytes, which represents the main reservoir of this virus, could explain the appearance of several immune-lymphoproliferative disorders. Among these, the MC is a benign B-cell lymphoproliferation that in some subjects can switch over to a frank lymphoma with different grades of malignancy (Table 1). MC is a common, but not necessarily constant manifestation of HCV-related lymphoproliferation. In this light, a previous history of MC and the subsequent appearance of B-cell NHL are not conflicting; they can represent two different clinical features of the same multistep process. In our experience, the B-cell lymphomas complicating MC show the same clinico-pathological and prognostic characteristics of idiopathic malignancies (Table 1). Similarly, a number of immunological symptoms, including the cryoglobulinemia, are frequently found in patients with B-cell malignancies. HCV may trigger a wide spectrum of immune system alterations, possibly due to variable combinations of unknown infectious, environmental, and genetic factors. An increased prevalence

Table 1. HCV Infection and Lymphoproliferative Disorders

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of Patients</th>
<th>HCV*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>WF Classification</td>
</tr>
<tr>
<td></td>
<td></td>
<td>L</td>
</tr>
<tr>
<td>MC</td>
<td>250</td>
<td>90</td>
</tr>
<tr>
<td>MC + B-cell NHL</td>
<td>15</td>
<td>100</td>
</tr>
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<td>Type C chronic hepatitis (CH)</td>
<td>500</td>
<td>100</td>
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<tr>
<td>Type C CH + B-cell NHL</td>
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<td>100</td>
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<tr>
<td>Type C CH + CLL</td>
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<td>100</td>
</tr>
<tr>
<td>Idiopathic B-cell NHL</td>
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<td>25</td>
</tr>
<tr>
<td>Chronic lymphocytic leukemia</td>
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<td></td>
</tr>
<tr>
<td>Controls</td>
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<td></td>
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<tr>
<td>Hodgkin's lymphoma</td>
<td>50</td>
<td>3</td>
</tr>
<tr>
<td>Immunologic diseases*</td>
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<td>6</td>
</tr>
<tr>
<td>Healthy controls</td>
<td>500</td>
<td>1.5</td>
</tr>
</tbody>
</table>

Abbreviations: HCV*, anti-HCV* (RIBA II) and/or HCV RNA* (polymerase chain reaction); WF, Working Formulation classification (L, low; I, intermediate; H, high grade).

* Systemic lupus, Sjögren's syndrome, rheumatoid arthritis, and systemic sclerosis.
of genotype 2a has been found in HCV-related MC.\textsuperscript{16} Moreover, the possible contribution of environmental and genetic factors is suggested by some interesting epidemiological observations: in chronically HCV-infected individuals, the presence of some extrahepatic manifestations, such as MC, autoimmune hepatitis, and probably B-cell NHL, is more frequently found in Italy and Southern Europe than in England and North America.\textsuperscript{15-18} We can hypothesise that the geographical heterogeneity of HCV-related disorders could also explain the different prevalence of HCV among Italian NHL series from different areas, namely the Northeast and center of Italy.\textsuperscript{1,5}

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REFERENCES


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