WALDENSTRÖM MACROGLOBULINEMIA: A ROLE OF HCV INFECTION?

To the Editor:

Waldenström's macroglobulinemia is a rare B-lymphocyte neoplasm characterized by monoclonal production of IgM Igs and by a marrow containing a diffuse infiltrate of plasmacytoid lymphocytes. The etiology of the disease is at present unknown, though epidemiological surveys suggested a possible role of the chronic antigenic stimulation. Because it is known that HCV infection is closely related with essential cryoglobulinemia (usually IgM), the presence of anti-HCV antibodies was investigated in a group of six patients affected by Waldenström's disease with a second-generation enzyme-linked immunosorbent assay. The diagnosis was previously assessed following standard criteria. In all the patients liver function tests were within the normal range and none of them underwent blood transfusions for the disease. Only two of six showed a slight positivity for the presence of antibodies against the C22c protein of HCV, while the others were negative. The presence of viral replication was subsequently determined by amplification of 5'NC region of HCV in the serum by nested polymerase chain reaction (PCR). In all six cases (100%) viral RNA was detected in serum. False positivity was excluded by the PCR amplification of the core region of the virus in the same sera. The HCV genotype was also obtained by PCR in three subjects according to Okamoto et al: two patients showed an infection by type II and one an unusual coinfection by four genotypes (I, II, III, IV).

The presence of HCV infection in Waldenström's macroglobulinemia was previously investigated by several researchers, but only with detection of anti-HCV antibodies. It is known that in monoclonal neoplasias the level of normal Igs is very low and an impaired synthesis of Igs occurs, therefore the level of anti-HCV antibodies can be under the detection limits of the usual methods. Only the use of the PCR allowed for detection of HCV infection in sera of subjects negative for anti-HCV antibodies. Furthermore, after a careful separation of the blood mononuclear cells, positive and negative (replicative) stranded forms of HCV were found in B lymphocytes of three patients, whereas monocytes and T lymphocytes were negative.

It is known that HCV is able to infect mononuclear cells of peripheral blood, but a direct involvement in B-cell neoplasias has never been established. The viral persistence in the immune system could greatly expand clones of Ig-producing cells, by a direct or indirect mechanism, and a mutational event can finally lead to the activation of oncogenes resulting in a plasma cell neoplasia. The appearance of monoclonal gammopathy in 10% of Aleutian minks chronically infected by the Aleutian disease virus could demonstrate this hypothesis.

The finding of HCV replication in benign (mixed cryoglobulinemia) and neoplastic (Waldenström's disease) IgM gammopathies suggests the need to investigate the possible role of HCV infection in all monoclonal diseases.

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