Mixed Cryoglobulinemia Associated with Hepatitis C Virus Infection

Key words: mixed cryoglobulinemia, hepatitis C virus, membranoproliferative glomerulonephritis, neuropathy

Cryoglobulinemia is a condition characterized by the presence of serum proteins that reversibly precipitate in the cold. Cryoglobulins are classified into three types: Type I consists of single monoclonal immunoglobulins without rheumatoid factor (RF) activity that are predominantly associated with malignant conditions of the immune systems; Type II and Type III are mixed cryoglobulins (1). Type II consists of polyclonal immunoglobulins and monoclonal immunoglobulins (usually, IgG and monoclonal IgM RF), and Type III consists of two or more polyclonal immunoglobulins. Clinically, mixed cryoglobulinemia (MC) has been made up of the essential MC, which is idiopathic, and secondary to various diseases, such as infectious diseases, autoimmune diseases, and malignant conditions.

The finding of a significantly high frequency of antibodies to hepatitis C virus (HCV) in essential MC was first reported in 1990 (2). Since then, the prevalence of anti-HCV antibodies has reportedly been estimated at 42 to 100% in patients with essential MC, and the percentage of HCV-RNA positive patients has been 63 to 100% in those patients (3). On the other hand, in 37 to 54% of patients with HCV infection, cryoglobulins were detected (4, 5). It has been found recently that peripheral blood mononuclear leukocytes, especially B lymphocytes, can be the site for extrahepatic viral replication of HCV (6). Therefore, it has been suggested that in patients with chronic HCV infection, direct active viral replication in B lymphocytes may induce the activation of clones of B cells and abnormal production of polyclonal RFs. In addition, unidentified factors might induce the switch to the production of monoclonal IgM RFs. Monoclonal IgM RFs binding to circulating polyclonal IgG or anti-HCV antibodies may play a role in the vascular and/or renal lesions (7). Recently, a high prevalence of anti-endothelial cell antibodies in MC with HCV infection was reported, and it suggested that these antibodies might be one of the causes of cryoglobulinemic vasculitis (8).

MC is a systemic disorder characterized by a typical triad: purpura, asthenia and arthralgia, and by severe vasculitis with involvement of kidneys, liver, nerves, and brain. Renal symptoms are usually a late manifestation of type II MC. Proteinuria with microscopic hematuria is the most frequent presenting renal syndrome, and is sometimes associated with signs of moderate chronic renal insufficiency (9). The histological finding is of a membranoproliferative glomerulonephritis (MPGN), with monocytes and neutrophil infiltration, and sometimes with a lobular pattern. Glomerular capillary thrombi or pseudothrombi, which consist of cryoglobulins or subendothelial deposits, are sometimes seen. Immunofluorescence examination shows subendothelial deposits of IgM, IgG, and C3, sometimes segmental (10). On the other hand, it was reported that HCV-infected patients with or without cryoglobulinemia showed MPGN, but IgM-RFs was detected in all of those patients (11). In the experimental mouse model recently developed, MPGN could be induced by intravenous injection of solublized cryoglobulins from patients with MPGN and HCV infection; still, intravenous injection of IgM-κ isolated from these cryoglobulins could lead to MPGN (12). Therefore, HCV, anti-HCV antibodies, and monoclonal IgM RFs may relate to the vascular and/or renal lesions.

Peripheral neuropathy associated MC has been widely reported since the first description (13). On histological examination, peripheral neuropathy has been classified into three types: axonopathy (axonal degeneration), myelinopathy (segmental demyelination), and interstitial neuropathy. MC patients clinically present as polynuropathies, sometimes as multifocal mononeuropathies, while axonopathy pattern is predominant on the electrophysiological and/or the histological examination (14). This axonal degeneration is thought to be due to ischemia following endoneural microangiopathy and vasculitis of epineural arteries (15). In MC patients with HCV infection, polynuropathies or multifocal mononeuropathies caused by sensory axonopathies were observed as the same as essential MC (16). However, compared with MC patients without anti-HCV antibodies, neuropathies were more severe, because of motor involvement, and in addition, vasculitis and alterations of endoneural microvessels were more frequently observed (16). On the other hand, a rare case of cryoglobulinemic neuropathy, presenting myelinopathy, with HCV infection was reported in this journal (17).

See also p 397.

Steroids and/or immunosuppressants (particularly cyclophosphamide) have been used to treat essential MC. In recent years, it has been reported that treatments with interferon-α had been beneficial for patients with cryoglobulinemia associated with HCV infection (18–20). In these trial data, the reduction of the serum cryoglobin concentration was accompanied by disap-
pearance of HCV-RNA, and MC relapsed causing the reappearance of virus, after discontinuation of interferon-α. Therefore, a large controlled trial in patients with MC and HCV infection is necessary to define the effects, including the prevention of relapse, of anti-viral agents.

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References